College of Health Sciences, Department of Adult Oncology.

A Retrospective Study on Treatment Response, Resectability and other Surgico-pathologic Outcomes of Locally Advanced Rectal Cancer Patients Treated with Neoadjuvant Chemoradiotherapy at Tikur Anbessa Specialized Hospital, Adult oncology unit.

Zerubbabel Ayalew (MD)

January 2022
Addis Ababa, Ethiopia

A Retrospective Study on Treatment Response, Resectability and other Surgico-pathologic Outcomes of Locally Advanced Rectal Cancer Patients Treated with Neoadjuvant Chemoradiotherapy at Tikur Anbessa Specialized Hospital, Adult oncology unit.

Advisor: Edom Seife (MD), Consultant oncologist, AAU CHS

Signature _____

Examiner: _____

Signature _____

Principal Investigator: Zerubbabel Ayalew (MD, Fourth Year Clinical Oncology Resident)

A Thesis Paper to be Submitted to AAU, Department of Clinical Oncology in Partial Fulfillment for the Specialty Certificate in clinical Oncology.

January 2022
Addis Ababa, Ethiopia

I. Acknowledgement

I would like to extend my deepest gratitude to Dr. Edom Seife (MD, clinical oncologist, AAU, CHS) for her enormous support starting from generating the idea of conducting a study on this subject matter to the development of a proposal and then writing this paper. I would like to thank all my colleagues who were involved and helped me in data collecting, recording, encoding, analyzing and writing this study.

II. Abstract

Background

Colorectal cancer is the third most diagnosed and second most important cause of cancer death worldwide. Rectal cancer is estimated to account for one third of all cases of colorectal cancer.(1) The treatment of rectal cancer is usually multimodal including surgery, chemotherapy, radiotherapy. The past 3 decades witnessed a significantly improved oncologic outcomes in patients with rectal cancer, which is mainly due to standardization of TME along with development of different neoadjuvant therapy strategies. (3) Despite these developments, our practice lacks adequate local evidences on which to base the treatment of our patients and this study aimed to address this issue.

We retrospectively collected data of 37 patients with rectal cancer who took neoadjuvant chemoradiotherapy at our setup. Great majority of patients had cT4b disease (60%; tumor invading in to adjacent pelvic structures); 56.8% of patients had cN2 and 86.5% had MRF positive disease. A little more than half (19) of the patients took induction chemotherapy followed by LCCRT. The clinical response (tumor down staging) rate was 40.6%. Resectability rate was 30%, APR was the most common surgery performed 9/11(81.8%), 63.6% had R0 resection.

Objective: to determine treatment response, resectability and other surgico-pathologic outcomes of rectal cancer patients treated with neoadjuvant chemoradiotherapy at TASH, adult oncology unit.

Method: A single institution based retrospective study was conducted at TASH adult oncology unit from October, 2014 to December, 2021. First the MRN of 205 patients who took more than 10 fractions of radiotherapy for rectal cancer from September, 2014 to December, 2021 were identified from radiotherapy logbook. After the charts of each patient were retrieved, 69 patients who took and completed radiotherapy as a neoadjuvant therapy were selected and entered in to data collection. Data was extracted using a tool prepared after evaluating pilot study on the charts of 5 patients. Only 37 patients fulfilled the inclusion criteria and included in this study. Basic descriptive analysis is used for describing the study population in relation to relevant variables.

Key words: Rectal cancer, Neoadjuvant chemoradiotherapy, clinical Stage, pathologic Stage, TASH, Ethiopia

III.Table of Contents

I. Acknowledgement.....iii

II. Abstract..... iv

I. List of Acronyms and Abbreviations.....3

Chapter One: Introduction.....5

1.1 Background..... 5

1.2 Statement of the problem..... 7

Chapter two: Literature Review.....8

2.1 Epidemiology.....8

2.2 Standard Treatment options.....8

2.3 Treatment Outcomes.....9

Chapter three: Objectives of the study..... 16

3.1 General Objective..... 16

3.2 Specific objectives..... 16

Chapter Four: Methodology.....17

4.1 Study Setting.....17

4.2 study design..... 17

4.3 Sources of data.....17

4.4 Source Population..... 17

4.5 Study Population.....18

4.6 Inclusion criteria..... 18

4.7 Exclusion criteria..... 18

4.8 Sample size determination and sampling procedure.....18

4.8.1 Sample size determination.....18

4.8.2 Sampling procedure.....19

4.9 Variables..... 19
4.9.1 Independent variables..... 19
4.9.2 Dependent variables..... 19
4.10 Operational definitions..... 19
4.11 Data collection tool and procedure..... 20
4.12 Data processing and Analysis..... 20
4.13 Dissemination of Result..... 21
4.14 Ethical Consideration..... 21
Chapter five. Result..... 22
5.1 Demographic Characteristics of Patients..... 22
5.2 Pre-neoadjuvant Therapy Clinical Profile of Patients..... 22
5.3 Neoadjuvant Therapy and Clinical Response Evaluation..... 24
Chapter Six. Discussion..... 28
Chapter Seven. Strength and Limitations of the Study..... 32
7.1 Strength..... 32
7.2 Limitations and Challenges..... 32
Chapter Eight. Conclusion..... 33
Chapter Nine. Recommendations..... 34
Chapter Ten. References..... 35
Chapter Eleven: Annex..... 38
Annex 1: Data Extraction Tool utilized in the study..... 38

IV. List of Acronyms and Abbreviations

2D RT: 2-Dimensional Radiotherapy…….……...…iii, 22, 27

3DCRT: 3-Dimensional Conformal Radiotherapy…….22, 27

5-FU: 5 Flourouracil…….…10, 13, 22

AAU: Addis Ababa University……. ii, iii

APR: Abdominoperineal Resection……...12, 24

cCR: Complete Clinical Response……..…….25

CCT: Consolidative Chemotherapy……..…….13, 25

CEA: Carcinoembryonic Antigen……...…….17, 21, 23

CHS: College of Health Sciences……..……. ii, iii

CRC: Colorectal Cancer……iv, 5, 6, 8, 13, 18

CRM: Circumferential Resection Margin…….…….7, 20, 23

CRT: Chemoradiotherapy……..…8, 9, 10, 11, 12, 14, 15, 17, 27, 28, 29, 31

DFS: Disease Free Survival……..…….11, 14

EMVI: Extramural Venous Invasion…..…….13

EUA: Examination Under Anesthesia …….……25, 28

IAEA: International Atomic Energy Agency…….……..……16

LAR: Lower Anterior Resection……..……24

LCCRT: Long Course Chemoradiotherapy……iv, 11, 12, 13, 15, 22, 24, 25, 26, 27

LCRT: Loong Course Chemoradiotherapy……..……9, 11, 22, 27

LRR: Locoregional Recurrence……..…….9, 14

MDT:Multidisciplinary Team ……..……..…….6, 24, 27, 29

MRF: Mesorectal Fascia…….……..…. iv, 8, 12, 13, 20, 23, 26

MRI: Magnetic Resonance Imaging…….7, 12, 13, 15, 17, 19, 20, 23, 25, 26

MRN: Medical Record Number……...……17

NACT:Neoadjuvant Chemotherapy…….14

OS: overall survival……..…….9, 10, 11, 12, 13, 14

pCR: Pathologic Complete Response…….…….11, 13, 15

RT: Radiotherapy……...…8, 9, 10, 13, 22, 24

SCRT: Short Course Radiotherapy……9, 11, 12, 13, 14, 22, 24, 25, 26

TASH: Tikur Anbessa Specialized Hospital…….. iv, 15, 16, 17, 19, 28

TME: Total Mesorectal Excision……iv, 8, 9, 10, 12, 13, 14, 15, 26, 31

TNT: Total Mesorectal Excision……12, 13, 14, 15, 2

Chapter One: Introduction

1.1 Background

Cancer is one of the foremost causes of morbidity and mortality worldwide. Its societal and economic impact will certainly rise as morbidity and mortality continue to increase and the demands on cancer services escalate.(4) Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020. (5) Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers. Lung cancer remained the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers. Overall incidence was from 2-fold to 3-fold higher in transitioned versus transitioning countries for both sexes, whereas mortality varied <2-fold for men and little for women.(1)

The global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020, with a larger increase in transitioning (64% to 95%) versus transitioned (32% to 56%) countries due to demographic changes, although this may be further exacerbated by increasing risk factors associated with globalization and a growing economy. (3)

Globally, CRC is the third most diagnosed and second most important cause of cancer death. In 2020 there were around 1.93 million new cases of colorectal cancer and 935, 000 deaths.(1) Rectal cancer is estimated to account for one third of all cases of colorectal cancer. According to Globocan 2020 report there were a total of 733,000 new cases of rectal cancer and associated 34,000 deaths.(5) A total of 70% of all CRC-related deaths occur in low- and middle-income countries. (2)

The burden of cancer will continue to shift to less-developed countries due to growth and aging of the population, lifestyle changes and increasing prevalence of known risk factors.(6) The geographical distribution of the burden of colorectal cancer is gradually shifting from countries with advanced economies to emerging countries. The possible reasons are aging population, an adoption of cancer- associated lifestyle,

exposure to different infections, including smoking, physical inactivity, and ‘‘westernized’’ diets.(7)

The incidence of colorectal cancer in sub-Saharan Africa is generally considered to be among the lowest worldwide; however, it is unclear whether this is due to poor epidemiological data or lower disease rates. The crude incidence of CRC in sub-Saharan Africa for both sexes is 4.04 per 100000 population (4.38 for men and 3.69 for women). Incidence increased with age with the highest rates in Southern Africa, particularly in South Africa.(8) Although the quality of epidemiological data is suboptimal, a recent study indicated that the incidence of colorectal cancer in sub-Saharan Africa is rising in most countries likely due to the rapid growth and aging of the population. Another reason could be marked increases in the prevalence of known or putative risk factors for cancer associated with westernization.(3,8)

In Ethiopia CRC is estimated to be the most common cancer among men and the 4th most common cancer in women with a crude incidence rate of 5.3 and 4.3 per 100,000 people respectively in men and women.(9) CRC is one of the commonest types of cancer in patients visiting our institution for cancer care.(10)

1.2 Statement of the problem

Rectal cancer accounts for one-third of CRC, and constitutes a major health concern world-wide. According to Globocan report there were a total of 733,000 new cases of rectal cancer and associated 340,000 deaths worldwide in 2020. (3) The effective treatment of CRC in sub-Saharan Africa is hampered by the advanced state of the disease at patient presentation. Incriminated factors are limited awareness of early signs and symptoms of cancer among the public and health care providers, lack of screening and early detection services, limitations on access to specialized care, as well as culture of stigma associated with diagnosis of cancer also plays a role in late-stage presentation in most parts of Africa including Ethiopia.(7)

Cancer care is not a "well practiced discipline" in Ethiopia. To this date there is only one well-equipped oncology center which gives both medical and radiation oncology services. There are few emerging centers across the country which have already started medical oncology services and working for the initiation of radiotherapy. Because of this and many other reasons, including absence of national cancer registry, literature regarding cancer and its care are scarce in Ethiopia. Hence our treatment strategies are solely dependent on evidences from mainly western setups. But these western treatment protocols are difficult to fully implement in our setup because of many reasons.

In our institution the treatment plan for locally advanced rectal cancer is decided with multidisciplinary discussion. Depending on the MDT decision patients are classified mainly in to two categories. The first category includes patients for whom the MDT decides to undergo upfront surgical resection without neo-adjuvant therapy. These are patients in whom the MDT decides upfront surgical resection with an assessment that surgical resection can be performed with negative surgical margins. The second category includes patients with a higher stage tumor in whom upfront surgery is avoided. In this group neoadjuvant therapy is administered before surgery. The purpose of this therapy is to down stage the tumor and to make it amenable for surgery with possible negative surgical margins.

Even if we follow such a trend of managing our patients with locally advanced rectal cancer, we do not exactly know the oncologic and surgical outcomes of our patients who took neoadjuvant therapy before surgery. This retrospective study will be the

first in its type to assess the efficacy of our neoadjuvant therapy. In addition, it will also help in generating institution-based evidence on how to manage our patients in the future.

Chapter two: Literature Review

2.1 Epidemiology

Anatomically the rectum starts at a virtual line from the sacral promontory to the upper edge of the symphysis pubis on MRI and ends at the superior border of the functional anal canal. (2)

Rectal cancer accounts for one-third of CRCs, and constitutes a major health concern world-wide. According to Globocan report there were a total of 733,000 new cases of rectal cancer and associated 340,000 deaths worldwide in 2020. (3) Adenocarcinoma is the commonest histologic type of rectal cancer accounting for a total of 95 % of all rectal cancers.

2.2 Standard Treatment options

Rectal cancer treatment presents a challenge, and its optimal management requires a multidisciplinary approach involving surgical, medical, and radiation oncologists (13). There have been only few prospective studies in sub-Saharan African related to CRC treatment(14). This pushes us to the edge of totally relaying on recommendations made by western institutions to manage our patients. According to current clinical practice guidelines, localized rectal cancer treatment relies on accurate staging procedures, which is highly dependent on pelvic magnetic resonance imaging. This allows the categorization of patients according to clinically defined risk categories. Each risk category may benefit from a specific type of treatment, for example, very early low grade cT1N0 tumor can be treated with local excision. Any tumor with a high stage needs to be treated aggressively with either upfront surgery or neoadjuvant therapy followed by surgery, namely, TME. Patients with high-risk features such as extramural vascular invasion, multiple nodal involvement (cN2 or positive extra-mesorectal node), cT4 or tumors close to or invading the MRF, a more intensive preoperative approach is recommended. Historically, local relapses in the pelvis occurred in more than one third of all patients with apparently localized rectal tumors. Neoadjuvant radiotherapy in rectal

cancer has been proven to be effective in reducing tumor burden in advance of curative surgery. The combination of postoperative radiotherapy and fluorouracil (FU) chemotherapy has been shown to reduce local recurrences and to improve survival for locally advanced rectal cancer. (3,13)

The outcome for patients with rectal cancer has significantly improved over the last thirty years. The last two decades have witnessed the development of a variety of preoperative RT and CRT schedules designed to optimize the sequence of treatment modalities and the most appropriate scheduling of RT and FU-based chemotherapy. Advances in surgical techniques, radiotherapy, and medical imaging technology have transformed the therapeutic landscape and have led to substantial improvements in sphincter preservation and local disease control. The standardization of total mesorectal excision was the first step to improve local control by reducing local relapses to less than 5%. Preoperative radiation, either short-course or long-course with concurrent administration of chemotherapy, was a second important step for reducing local relapses to a minimum, even in locally advanced tumors where a clean surgical resection was not possible or would not be curative. However, only the Swedish Rectal Cancer Trial, which evaluated a short course of preoperative irradiation (25 Gy, delivered in five fractions), found an advantage in overall survival.(3,11, 12, 14)

The choice of therapeutic approach for rectal cancer is based on several factors; whether trimodality therapy (surgery, radiotherapy, and chemotherapy) is used depends greatly on tumor stage and the location of the tumor in the rectum. Thus, accurate preoperative evaluation and staging of rectal cancer is, perhaps, the most critical step in the management of this disease. For patients with locally advanced rectal cancer, preoperative chemoradiotherapy (CRT) and short course radiotherapy (SCRT) have been established as alternative standards of care. Currently, the only definitive indication for the use of neoadjuvant therapy in rectal cancer is the presence of a T3, T4, or node-positive tumor. (11)

2.3 Treatment Outcomes

The widely accepted standards of care for locally advanced rectal cancer consists of neoadjuvant LCRT or short-course (hypo-fractionated) radiotherapy (SCRT) followed by TME and adjuvant fluoropyrimidine based chemotherapy. While SCRT is best suited for tumors with a stage not more than T3, LCRT can be used for all patients

with locally advanced rectal cancer who has no a contraindication to take chemotherapy.

Preoperative SCRT (25 Gy of irradiation delivered in 5 daily fractions with no concurrent chemotherapy) is commonly practiced in northern Europe in stage II-III rectal cancer patients. Several SCRT randomized trials have demonstrated the importance of preoperative RT plus TME in reducing LRR, in stage II and III rectal cancer patients. The Dutch rectal cancer trial, the Swedish rectal cancer trial, and the MRC CR07 trials all compared the outcomes of locally advanced rectal cancer patients who were treated with preoperative SCRT followed by radical surgery versus surgery alone and concluded that preoperative SCRT significantly decreased local recurrence even in TME resected patients across all the three trials. The Swedish rectal cancer trail showed a statistically significant improvement in OS (5-year OS rate of 58% vs. 48 % p = 0.004 in favor of preoperative SCRT) but this trial is criticized for using a non-TME surgery which may be the reason why OS improvement is demonstrated only on this trial. (13,15,16)

The other neoadjuvant treatment modality is long course chemoradiotherapy. This treatment paradigm consists of around 6 weeks of neoadjuvant CRT (infusional 5-FU or oral capecitabine concurrent with RT), followed by 6 or more weeks of recovery prior to surgery (usually TME). Several studies investigated pre- and postoperative CRT in patients with locally advanced rectal cancer, with the aim of determining the best sequence of CRT administration with surgery. Despite researchers' best earlier efforts, the optimal sequence did not become clear until results from the German Rectal Cancer Study Group trial became available in 2004. This seminal trial firmly established the role of neoadjuvant CRT by directly comparing preoperative with postoperative CRT for locally advanced rectal cancer.(11,12)

The German Rectal Cancer Study Group trial was initiated in February 1995, and enrollment was extended through September 2002. The study enrolled 823 patients with clinical stage T3 or T4 or node-positive disease. Patients were then randomly assigned to receive either preoperative (n = 421) or postoperative (n = 402) CRT. The preoperative treatment consisted of 5,040 cGy delivered in fractions of 180 cGy per day, 5 days per week, concurrently with infusional 5-FU (1,000 mg/m daily for 5 days during the first and fifth weeks of RT). All patients underwent TME 6 weeks after the completion of CRT. One month after this surgery, 4 additional cycles of adjuvant 5-FU (500 mg/m bolus daily for 5 days, every 4 weeks) were administered. CRT was

identical in the postoperative treatment group, except for the delivery of a boost of 540 cGy in the latter group.

The primary endpoint of this trial was OS.(17) The overall five-year survival rates were 76% and 74%, respectively (p = 0.80). The five-year cumulative incidence of local relapse was 6 percent for patients assigned to preoperative chemoradiotherapy and 13 percent in the postoperative-treatment group (p = 0.006). There was also a significant difference in sphincter preservation in favor of preoperative chemoradiotherapy 39% vs.19% (p = 0.004). (17) Pathologic complete response was achieved in 8% of patients in the preoperative CRT arm. According to intention-to-treat analysis, OS at 10 years was 59.6% in the preoperative arm and 59.9% in the postoperative arm (p = 0.85). The 10-year cumulative incidence of local relapse was 7.1% and 10.1% in the pre- and postoperative arms, respectively (p = 0.048). No significant differences were detected for 10-year cumulative incidence of distant metastases (29.8% and 29.6%; p = 0 .9) and disease-free survival.(16)

The other trial comparing preoperative and postoperative CRT in locally advanced rectal cancer was NSABP-R03. It analyzed data on 123 patients randomly assigned to preoperative and 131 to postoperative chemoradiotherapy. Surviving patients were observed for a median of 8.4 years. The 5-year DFS for preoperatively treated patients was 64.7% vs. 53.4% for postoperative patients (p = 0.011). The 5-year OS for preoperative patients was 74.5% vs. 65.6% for postoperatively treated patients (p = .065). A complete pathologic response was achieved in 15% of preoperative treatment arm patients. (18)

The chemotherapies of choice that are commonly used in the concurrent CRT are either continuous infusion 5 FU or oral capecitabine. This agents were compared head to head in a phase III randomized clinical trial and resulted in a comparable outcome with a different toxicity profile.(19) Intensification of the CRT was also tried with the addition of oxaliplatin to CI – 5 FU or oral capecitabine with the hope that it may lead to a better outcome. No significant differences in the rates of pCR, sphincter-sparing surgery, surgical down staging or locoregional control were identified between the CI-5FU and capecitabine regimens with or without oxaliplatin. Pathologic complete response was 21% vs 18%. The 3-year incidence of any locoregional events was 12% vs 11% and OS rates were also comparable 81% vs 80%. Patients treated with oxaliplatin experienced significantly more grade 3 or 4 toxicities namely neuropathy and diarrhea (p < .001). (20)

The other issue commonly discussed in neoadjuvant therapy of locally advanced rectal cancer is the choice of long course chemoradiotherapy (LCCRT) vs. short course radiotherapy (SCRT). The enrolled population in clinical trials assessing the efficacy of the two approaches was not completely comparable considering that the SCRT regimens included patients with early tumor (stage T1 – T2 and some resectable T3), while LCRT studies considered mainly more locally advanced rectal cancer patients (T3, T4 and unresectable tumors). (14) The assumption that adding chemotherapy to long course (45 - 50 Gy) preoperative radiotherapy could increase the local effect of radiotherapy, led to the comparison between radiotherapy and chemoradiotherapy as neoadjuvant regimen.

Although LCRT was expected to have advantages of higher sphincter preservation and lower complication rates, several phase III randomized studies have found no differences in oncological outcomes (DFS, OS, local relapse-free survival). However, LCRT schedule showed higher pathological complete response (pCR) rate and clear resection margin. (21) Two main clinical trials addressed this issue by comparing the two approaches head-to-head, which demonstrated comparable outcomes in major oncologic outcomes with a difference in treatment related toxicities between the two approaches. The rate of pathologic complete response was 1% vs 16% in the polish trial and 1% vs 15 in the TROG trans-Tasman trial both in favor of LCCRT. Evidence from these trials and other studies shows that either of the two neoadjuvant therapy modalities can be used for appropriately selected patients.(18,19) Even if not supported with a clear evidence from a well-designed clinical trial, there is a consensuses among experts to use peoperative CRT in patients who have a distal rectal tumor for which an APR is believed to be necessary. The use of CRT prior to surgery could convert an APR to a sphincter-preserving operation, such as a low anterior resection with coloanal anastomosis, which has the potential to profoundly improve a patient's quality of life.(13)

While these multimodal approaches discussed above have led to improvement in the rates of local recurrence, it has not had significant effect on the rates of distant relapse or OS over standard TME surgery alone.

More recently a newer approach (TNT) of treating locally advanced rectal cancer patients with a **"pelvic MRI-defined high-risk features"** of systemic metastasis has emerged. These patients have peculiar high-risk features on pelvic MRI: T4, T3 tumors invading 5 mm or more of mesorectal fat pad, particularly those that involve

or reach with in less than 1 mm of the MRF, EMVI, N2 and/or extra-mesorectal nodal involvement. After the commonly practiced standard of care, metastasis is more frequently seen during follow up. In such patients administering neoadjuvant chemotherapy along with preoperative LCCRT or SCRT before surgery provides a better way of targeting systemic micro-metastases early in the course of treatment and hence good control of systemic relapses.

The potential benefits of TNT include better compliance than postoperative chemotherapy, a higher pathological complete remission rate which may facilitates a non-surgical approach, and earlier treatment of micro-metastatic disease with improved disease-free survival compared to standard preoperative chemoradiation or short-course radiation.(23)

This premise of using TNT in select group of patients is supported with two recently published phase III randomized clinical trials, RAPIDO and PRODIGE 23.These trials showed that adding neoadjuvant chemotherapy to either standard SCRT or standard LCCRT in locally advanced rectal cancer patients with high risk features of distant relapse reduces the risk of metastasis and significantly prolongs disease-related treatment failure and disease-free survival.(21, 22)

The issue of TNT was first formally addressed in the phase III Polish II trial which aimed to evaluate whether preoperative SCRT followed by consolidation chemotherapy was superior to preoperative chemoradiation in patients with unresectable cT4 or fixed cT3 rectal cancer. It assigned (with 1:1 randomization) 541 patients from 39 Polish institutions in to either preoperative 5x5 Gy followed by 3 cycles of FOLFOX4 or to chemoradiation (50.4 Gy with bolus 5-FU, leucovorin and oxaliplatin). Majority of the patients (n = 515) were eligible for analysis: 261 in the SCRT/CCT group and 254 in the chemoradiation group. The primary end point of the study was R0 resection rate. Early reports showed no differences in R0 resection rate (77% vs. 71%, p=0.07) and postoperative complications. Acute toxicity was lower in the SCRT/CCT group, p=0.006. The pCR (ypT0N0) 16% vs. 12%, p=0.17, and sphincter-preserving surgery was done 62% vs. 59%. OS benefit was observed in the SCRT/CCT group, 8% difference at 3 years (p = 0.046). This difference in overall survival disappeared later at 8 years (48.8% vs.48.6%, HR=0.90, p=0.38). From this study a conclusion was made: no difference in OS and late complications between the two groups. Nevertheless, SCRT/CCT may be considered as an alternative to long

course chemoradiation with lower acute toxicity cost-effectiveness and convenience.(26)

The second study on major and land mark trail on TNT is the phase III open-label, multi-center randomized RAPIDO trial. Patients with a biopsy proven newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria: cT4a or cT4b, EMVI, cN2, involved MRF, or enlarged lateral lymph nodes), were eligible for the study. A total 0f 920 patients were included with a 1:1 randomization. Patients allocated to the experimental treatment group received SCRT (5×5 Gy over a maximum of 8 days) followed by 6 cycles of CAPOX or 9 cycles of FOLFOX4 followed by TME. Choice of CAPOX/FOLFOX4 was per physician discretion or hospital policy. Patients allocated to the standard of care group received a RT of 50.4 Gy in 28 fractions or 50 Gy in 25 fractions with concomitant capecitabine followed by TME and, with or without adjuvant 8 cycles of CAPOX or 12 cycles of FOLFOX4.

The primary endpoint of the study was 3-year disease-related treatment failure (DrTF), defined as the first occurrence of LRF, distant metastasis, new primary CRC, or treatment-related death, assessed in the ITT population. After a median follow-up of 4.6 years the 3-year DrTF was 23.7% versus 30.4% favoring the TNT group (HR= 0.75, p = 0.019). Distant metastasis caused most disease-related treatment failures. At 3 years, the cumulative probability of distant metastases was 20 % in the experimental group compared with 26.8% (22.7 – 30.9) in the standard of care group (HR = 0.69; p = 0.0048). The cumulative probability of LRF at 3 years was 8.3% in the experimental group compared with 6 % in the standard of care group (HR = 1.42; p = 0·12). The rate of cPR was significantly higher in the TNT arm which was 28% versus 14% (p < 0.0001). Both groups had similar OS rate at 3 years 89.1% versus 88.8% (HR = 0.92; p = 0.59). (25)

This approach of managing locally advanced rectal cancer is now accepted by NCCN as a category 2A recommendation; and the SCRT can be used either before or after the neoadjuvant chemotherapy.(27)

Another phase III clinical trial (UNICANCER-PRODIGE 23) randomized 461 patients to either the neoadjuvant chemotherapy group (n = 231) or the standard of care group (n=230). Patients were 18 -75 years old, newly diagnosed, biopsy-proven, rectal adenocarcinoma staged cT3 or cT4 M0, with a WHO performance status of 0 - 1. The neoadjuvant chemotherapy group received 6 rounds of FOLFIRINOX given

every 14 days, CCRT, followed by TME, and then adjuvant chemotherapy (3 months of modified FOLFOX6. The standard-of-care group received CCRT, followed by TME and then adjuvant chemotherapy (for 6 months). In both the groups CRT consisted of 50 Gy over 5 weeks (2 Gy per-fraction five times per week, with a reduction in fields after 44 Gy) and concurrent oral capecitabine (800 mg/m^2) twice daily for 5 days per week.

The primary endpoint of the study was DFS assessed in the ITT population at 3 years. At a median follow-up of 46.5 months, 3-year DFS rates were 76 % in the experimental group and 69% in the standard-of-care group (HR = 0.69, p = 0.034). The 3-year OS rates were 91% in the NACT group and 88% in the standard of-care group. Distant metastasis caused most recurrences 17% in the NACT group versus 25% in the standard-of-care group. Three-year metastasis free survival rates were 79% in the NACT group and 72% in the standard of care group. No differences were seen in overall LRR rates between the groups 4% vs. 6% (HR 0.78, p = 0.56). The rate of cPR was also was higher in the NACT arm; 25.5 % vs 11.7 %, p < 0.001.(28)

The above two studies provided **practice changing evidences in favor of TNT** on how to manage patients with locally advanced rectal cancer, especially in those patients who have **"pelvic MRI defined high risk features"** of distant metastasis.

Another option of TNT though not commonly practiced is administering neoadjuvant chemotherapy followed by LCCRT which is a different sequencing of neodjuvant therapy compared to the discussed trails. This approach was studied retrospectively at MSKCC in patients with clinical stage II/III rectal cancer (T3/4, N1–2 based on endorectal ultrasound or MRI). Over a period of 5 years, 57 patients received induction chemotherapy in the form of FOLFOX (median 7 cycles) then CRT. From these patients 9(15.8%) had a complete clinical response, 1 patient developed metastatic disease. Forty-nine patients undergone TME, all had R0 resections, 23 (47%) had tumor response > 90%, including 13 (27%) pCR. (29) Though we have been using this approach for the past 6 to 8 years in our institution, its efficacy is not studied and hence unknown. Addressing this issue is the main aim of this study.

Chapter three: Objectives of the study

3.1 General Objective

To assess the treatment response, resctability and other surgicopathologic outcomes of rectal cancer patients treated with neoadjuvant therapy at Tikur Anbessa Specialized Hospital (TASH).

3.2 Specific objectives

- To determine the clinical response rate to neoadjuvant therapy in locally advanced rectal cancer patients taking neoadjuvant therapy in TASH.
- To assess the rate of resectability in locally advanced rectal cancer patients managed with neoadjuvant therapy in TASH.
- To determine the pathologic response rate to neoadjuvant therapy in locally advanced rectal cancer patients taking neoadjuvant therapy in TASH.
- To determine the rate of negative surgical resection margin in locally advanced rectal cancer patients treated with neoadjuvant therapy in TASH.
- To determine the rate of sphincter preservation in locally advanced rectal cancer patients treated with neoadjuvant therapy in TASH.

Chapter Four: Methodology

4.1 Study Setting

The study is carried out in adult oncology department of Tikur Anbesa Specialized Hospital (TASH), under the Addis Ababa University. TASH is a teaching, central tertiary generalized referral hospital built in the early 1960's. The hospital has about 800 inpatient beds and it gives a multifaceted service including treating oncology patients. The radiotherapy center was established some 23 years ago by the help of IAEA. It is the only radiotherapy center for patients coming from the all corners of the country. The adult oncology department has currently six full time oncologists, three physicists, five radiotherapists, thirty-eight residents and other supportive staffs. Other staff members include clinical oncology nurses, social workers, chart keepers, secretaries and cleaners. The department gives an outpatient service for all kinds of solid tumors, selected hematologic malignancies and an inpatient service with 19 beds.

A newer satellite center outside the compound is also used for inpatient and outpatient oncology service. It has 16 more inpatient beds for adult oncology patients. The adult oncology department provides radiotherapy, chemotherapy and palliative care services for cancer patients.

Currently the radiotherapy service is being given with one Linac radiotherapy machine and another Cobalt-60 is on maintenance. There is one intracavitary brachytherapy machine for the treatment of cervical cancer and endometrial cancer.

The center aspires to become a center of excellence in the diagnosis, treatment and care of patients with cancer

4.2 study design

An institution based retrospective study.

4.3 Sources of data

Data was collected from patients' charts and log books.

4.4 Source Population

Source population is all cancer patients treated at TASH, Radiotherapy Center (adult oncology department) from September, 2014 to November, 2021

4.5 Study Population

Histologically confirmed cases of rectal cancer who received neoadjuvant therapy at TASH, adult oncology from September, 2014 to November, 2021.

4.6 Inclusion criteria

All charts of patients with histo-pathologically confirmed rectal adenocarcinoma who are treated with neoadjuvant therapy from January 2014 to November, 2021

4.7 Exclusion criteria

Those patients who didn't complete the neoadjuvant therapy

Those patients who had no appropriate response evaluation and/or surgery after completion of the neoadjuvant radiotherapy.

Those patients who lack adequate clinical, laboratory and imaging information.

Those patients who have incomplete medical records (i.e., like unknown stage of the disease, unknown neoadjuvant treatment modality the patient took etc.)

4.8 Sample size determination and sampling procedure

4.8.1 Sample size determination

Sample size calculation: using the single population proportion formula, with an anticipated resectability rate of 50%.

$$\boldsymbol{n = \frac{(Z_{1-\alpha})^2)P(1-P)}{d^2}}$$

n = minimum sample size required for the study

$Z_{1-\alpha}$ = standard normal distribution with confidence interval of 95%, $Z = 1.96$

d = absolute precision or tolerable margin of error ($d = 0.05$)

p = the anticipated resectability rate in the sample population in this study

Since there is no similar study conducted previously in Ethiopia, the probability of resectability is taken as 50% ($p = 0.5$).

Therefore, the sample size required for the study is calculated as follows

$$n = \frac{1.96^2(0.5)(0.5)}{0.0025} = \frac{0.9604}{0.0025} = 384$$

The calculated sample size becomes 384. When 10 % is added for contingency that may happen due lost chars or incomplete reports and finally got a sample size of 422.

But because of many reasons it is clear that we can't get this number of patients with locally advanced rectal cancer who are treated with neoadjuvant radiotherapy in our institution, so all patients with locally advanced rectal cancer treated with neoadjuvant CRT at TASH from September, 2014 to December 2021 who can pass the exclusion criteria are included in this study.

4.8.2 Sampling procedure

Patient MRN numbers and names registered from September 2014 to December 2021 were identified from log books. Patients' charts were retrieved using their MRN and the eligible charts were selected with thorough chart review. Radiotherapy treatment sheets were also identified and used for data collection in most of the patients.

4.9 Variables

4.9.1 Independent variables

Neoadjuvant chemoradiotherapy patients took
Initial stage of the tumor (both TNM and Group staging)
Pretreatment value of serum CEA
Patients' sex and age

4.9.2 Dependent variables

Clinical response rate
Rate of resectability
R0 resection rate
Pathologic response rate

4.10 Operational definitions

Rectal cancer: here on the study the term rectal cancer is used to describe rectal adenocarcinoma

Clinical stage: The anatomic extent of the disease as determined by clinical means, staging workup with physical examination and imaging(s) like CT scan, ultrasound, MRI, X-ray.

Histopathology: refers to microscopic study of tissue/tumor specimen from biopsy or surgical specimen.

Clinical response rate: The method to monitor how the cancer is responding to the treatment provided, from information acquired clinically, by imaging and/or tumor

markers. Here in our study, the extent of change in clinical T and N category is used to asses clinical response rate. In this study the main aim is to see the down staging effect of the neoadjuvant therapy on the tumor. One or more stage decrement in the clinical T stage is taken as tumor down staging or a partial response. Regarding nodal category, a change from a positive clinical nodal status to a negative clinical nodal status is taken as a down staging. A change of CRM status from positive to negative is taken is also taken as a down staging effect. Complete clinical response (cCR) was defined as no visible tumor on imaging with pelvic CT or MRI along with negative metastatic workup.

Pathologic response rate: the criteria described for the clinical response evaluation are used the same to the pathologic response rate evaluation.

Treatment completion: in this study patients who took at least 40 Gy of radiotherapy are considered as completed as their treatment.

R0 resection rate: the rate of undergoing a radical surgery with all surgical (proximal, distal and circumferential) margins being negative

TNM stage: T describes size of the tumor and spread to nearby tissue, N describes spread of cancer to nearby lymph nodes, M explains the distant spread to other parts of the body

Group stage: this explains the combined score of TNM stage

Pathologic stage: the stage of the tumor as explained by a pathologist after examination of the surgically resected specimen

4.11 Data collection tool and procedure

Data was collected from patients' medical record charts using a structured data collection tool containing closed and open-ended questions specifically designed for the study.

The tool was prepared by using 5 charts as a pretest; data was collected from the medical chart of each participant by two trained health professionals, under close supervision and facilitation by the principal investigator. Each day, the collected data was checked for accuracy and completeness.

4.12 Data processing and Analysis

The revised patient record charts were checked for completeness, cleaned manually and entered in to Epidata version 4.6 and then transferred to SPSS version 26 for further analysis. Basic descriptive analyses like frequency, proportion mean and

median will be done. Clinical response is evaluated by means of determining the degree of downstaging in TNM stage of the rectal tumor as the RECIST criteria is difficult to implement in CRC.

4.13 Dissemination of Result

The findings of this study will be submitted to department of clinical oncology of college of health sciences, Addis Ababa University as a partial fulfillment of specialty degree in Clinical Oncology. The outcome of this study will be presented at annual oncologic conference. Finally, the manuscript will be submitted to scientific journals for possible publication.

4.14 Ethical Consideration

Ethical clearance was obtained from Ethical Review Committee of Clinical Oncology Department of the college. Permission letter was submitted to the medical record unit from the Clinical Oncology Department & Research Directorate to retrieve and review the charts. Confidentiality of the information was maintained throughout the study by excluding names as identification in the data extraction form and the data will be used only for the purpose of the proposed study.

Chapter five. Result

5.1 Demographic Characteristics of Patients

This study included the results of 37 patients with locally advanced rectal cancer who received neoadjuvant therapy at TASH adult oncology unit from September 2014 to December 2021. A total of 69 such patients were identified, and 32 patients were excluded from the study as they didn't fulfill the inclusion criteria. Among the studied patients the majority (24; 65%) were males. About half (17) of the patients were 50 years old or younger. The age distribution ranges from 17 year to 70 year, the median age of presentation being 42 years.

Table 1. The demographic characteristics of patients included in this study

Variable (n = 37)		Frequency	Percent (%)
Sex	Male	24	64.9
	Female	13	35.1
Age strata in years	< 25	5	13.4
	26 – 40	10	27
	41 – 50	9	24.3
	51 – 60	9	24.3
	> 60	4	11

5.2 Pre-neoadjuvant Therapy Clinical Profile of Patients

Primary tumor staging was done with pelvic MRI in 26 patients (70.3%), pelvic CT scan was used in 10 (29.7%) patients the remaining one patient was staged with intraoperative findings. Majority of the patients 22 (59.5%) presented with T4b, and 12 (32.4%) had T3 disease; the rest of the patients 3 (8.1%) had T4a disease. A little more than half (21, 59.5%) of the patients had N2 disease, 11 patients had N1 and 4 patients had N0 disease, while 1 patient had unknown nodal disease status before the neoadjuvant therapy. The MRF was involved by the tumor in 32 patients (86.5%), it was free of tumor in 3 patients (8.1%), and undetermined in 2 (5.4%) patients. Low rectal tumor was the most common 22 patients (59.5%).

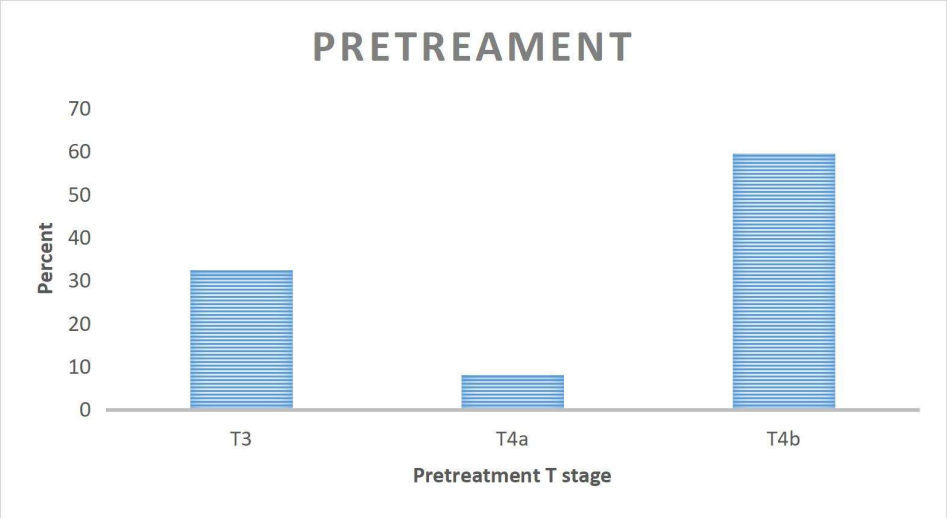

Figure1: Bar-graph that shows the baseline cT stage distribution.

Table 2: Pre-neoadjuvant clinical characteristics of patients

Variable (n = 37)		Frequency	Percent (%)
Clinical Variable	Pelvic MRI used	26	70.3
	Pelvic CT scan used	10	27
	Intraoperative finding	1	2.7
cN Stage	N0	4	10.8
	N1	11	29.7
	N2	21	56.8
	Unknown	1	2.7
MRF/CRM status	Positive/involved	32	86.5
	Negative	3	8.1
	Unknown	2	5.4
Location of the primary tumor in the rectum	Upper rectum	3	8.1
	Mid-rectum	5	13.5
	Low-rectal	22	59.5
	Involved multiple regions of the rectum	7	18.9
Serum CEA level	≤ 5 ng/ml	17	46
	> 5 ng/ml	18	48.6
	Unknown	2	5.4

Abdominal CT scan was used for metastatic workup in 28 patients (75.6%), abdominal ultrasound was used in 9 (23.4%) patients. Chest X ray alone was used to rule out lung metastasis in 31(83.8%) patients and 6 (16.2%) patients required chest CT scan in addition to chest X ray to rule out lung metastasis.

Histologically 4 patients had mucinous adenocarcinoma, 3 patients had signet ring cell adenocarcinoma, 1 patient had undifferentiated carcinoma, 29 patients were stated to have just adenocarcinoma. Majority 22 (59.5%) of the patients had a tumor of unknown grade, 11 patients had well-differentiated adenocarcinoma, 3 patients had moderately differentiated tumor, 1 patient had undifferentiated carcinoma.

The baseline serum CEA level was 5 ng/ml or less in 17 patients, more than 5 ng/ml in 18 patients and undetermined in 2 patients.

Table 3: Tumor histology as per colonoscopic biopsy

Variables (n = 37)		Frequency	Percent (%)
Histologic type	Adenocarcinoma	29	78.4
	Mucinous adenocarcinoma	4	10.8
	Signet ring cell adenocarcinoma	3	8.1
	Undifferentiated carcinoma	1	2.7
Histologic grade	Well differentiated	11	29.7
	Moderately differentiated	3	8.1
	Undifferentiated	1	2.7
	Unknown grade	22	59.5

5.3 Neoadjuvant Therapy and Clinical Response Evaluation

The time gap between the initial staging of the disease and initiation of neoadjuvant radiotherapy was 19.5 ± 14.6 weeks; ranging from a minimum of 1 week up to a maximum of 52 weeks. The overall treatment time in patients in LCCRT or LCRT cohort ranges from 5 to 12 weeks, and the mean was 6.9 ± 1.4 weeks.

About 19 (51.4%) patients took induction chemotherapy followed by long course chemoradiotherapy. The next most frequent (16, 43.2%) form of neoadjuvant therapy was long course chemoradiotherapy, 1 patient took long course radiotherapy only and the other one undergone short course radiotherapy. FOLFOX was the most commonly used induction chemotherapy followed by CAPEOX and the other regimen used was

5-FU/LV. Near to two thirds of the patients were treated using conventional/2D radiotherapy.

Table 3: Type of neo-adjuvant therapy patients took.

Type of neoadjuvant therapy & RT technique used (n = 37)		Frequency	Percent (%)
Neoadjuvant therapy	LCCRT	16	43.2
	Induction chemotherapy followed by LCCRT	19	51.4
	LCRT	1	2.7
	SCRT	1	2.7
Radiotherapy technique used	Conventional/2D RT	24	64.9
	V-Sim/3D RT	7	18.9
	3DCRT	6	16.2

Clinical staging evaluation after neoadjuvant therapy is depicted in the table below. Pelvic MRI with or without abdominopelvic CT scan was used for locoregional disease staging in 30 (81.1%) patients. Only abdominopelvic CT scan was used in 7 patients. Two patients were found to have distant metastasis one with lung secondary and the other one metastasis to the liver. Post neoadjuvant serum CEA value was determined in only 25 patients; 17 patients had ≤ 5 ng/ml and the remaining 8 patients had a value of ≥ 5 ng/ml.

Table 4: Post Neoadjuvant Therapy Clinical Staging of Patients

Variables	Clinical stage	Frequency	Percent (%)
cN stage	N0	13	35.1
	N1	13	35.1
	N2	8	21.6
	Unknown	3	8.1
cM stage	M0	35	94.6
	M1	2	5.4
	Unknown	0	0

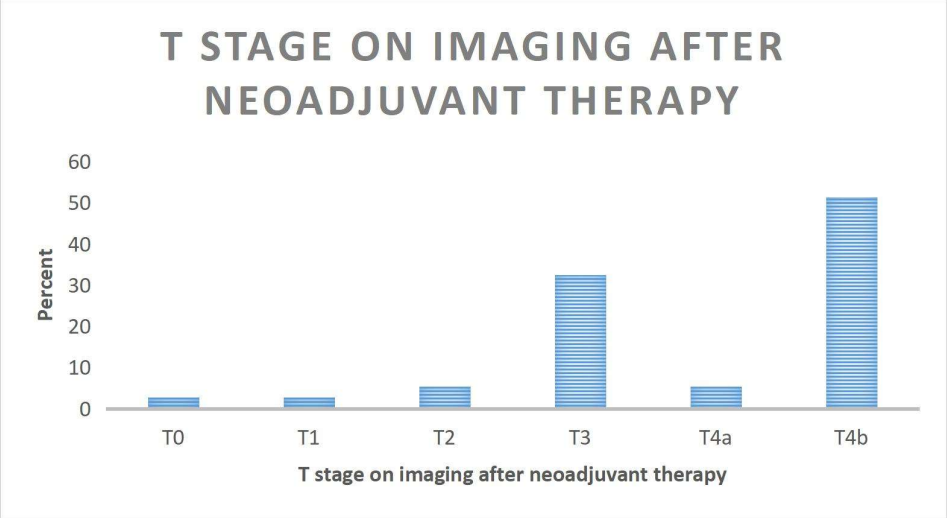

Figure 2: Bar-graph shows the post-neoadjuvant therapy cT stage distribution.

The time gap between completion of neoadjuvant chemoradiotherapy and response evaluation by imaging in the LCCRT cohort was 8.8 ± 7.2 weeks with the minimum of 3 weeks and the maximum being 45 weeks. The patient treated with SCRT completed it over a course of 5 days, there was no response evaluation by imaging after the SCRT.

Curative resection was done in 11 patients, 10 patients from the cohort who took neoadjuvant chemoradiotherapy; the remaining one patient took SCRT. The time gap between completion of RT and surgery ranged from 10 weeks to 58 weeks, the mean being 18 ± 14.4 weeks. The one patient who took SCRT undergone surgery 17 weeks after the final day of RT. APR was done for 9 patients and LAR for the rest 2 patients. In those patients who had no surgery the reasons were as follows; 16 patients were declared unresectable either on MDT discussion or EUA. In 5 patients there was no clear reason mentioned. Two patients refused surgical resection (1 had cCR); the other 2 patients found to have distant metastasis up on treatment response evaluation.

Postsurgical pathologic report was evaluable in 10 patients. Only two patients had complete pathologic report. Five patients had pT3, 4 patients pT2, and one patient pT4a pathologic T stage. Three patients were stated to have pN0, even if inadequate number of lymph nodes were reported in all of the 3 patients. Five patients had a report of ypNx with nothing mentioned about lymph nodes. Two patients had sufficient ypN reported; one pN1 and the other pN2a. Regarding surgical margin status, 7 patients had negative proximal, distal and circumferential margins. All the 3

surgical margins are unknown in 2 patients. One patient was reported to have negative proximal and distal margins but a positive circumferential margin.

Table 5: Comparison of pre- vs. post-neoadjuvant therapy radiologic and pathologic stages

Stage	Pre-neoadjuvant therapy	Post-neoadjuvant therapy radiologic stage	Pathologic report
T0		1	
T1		1	
T2		2	4
T3	12	12	5
T4	25	21	1
N0	4	13	3
N1	11	13	1
N2	21	8	1
NX	1	3	5
CRM Involved	32	22	1
CRM Free	3	12	7
CRM status unknown	2	3	2

Chapter Six. Discussion

Compared to the known studies done on neoadjuvant therapy in locally advanced rectal cancer, the 37 patients included in this study have a significantly different demographic and clinical profile. To start with, the patients in this study were younger than those involved in the German rectal cancer trial, Polish-II, RAPIDO and PRODIGUE-23 trials. The median age of patients involved in our study is 42 years whereas it is 62 years for those mentioned standard trials. The male to female ratio is almost similar to these studies (65% to 35%).

The pretreatment clinical profile of the patients in our study more or less matches to Polish-II trail. Pelvic MRI was used for baseline loco-regional staging in 70.3% of our patients comparable to the Polish-II study where 65% had pelvic MRI done for initial staging of the primary tumor extent. Pretreatment pelvic MRI was mandatory in all studies used here for comparison, including the study done at Alexandria university, Egypt, MSKCC study, the RAPIDO and PRODIGUE-23 studies. In addition to the pelvic MRI endorectal ultrasound is also used in many patients. No one patient from our study had endorectal ultrasound exam.

Most of our patients were unresectable at presentation; similar to the patients in Polish-II study. Polish-II compared LCCRT vs. SCRT/CCT for unresectable, cT4 or fixed cT3 rectal cancer. While similar to the patients in Polish-II trial, our patients had a relatively far advanced disease compared to the patients studied in PRODIGUE-23 and RAPIDO. In our study about 67.6% of patients had cT4 disease, 32.4% of patients had cT3 disease which is similar to the Polish-II study. Among the 541 patients who were assigned to the Polish-II trial, 65% had cT4 and 33% had cT3 disease, which almost matches to our patients' profile. This figure is 36.7% and 63.3, in the Alexandria university study, 31% & 66% in the RAPIDO trial, 18% & 83% in the PRODIGUE-23 trial respectively. In a retrospective study done on 49 patients at MSKCC, cT4 disease was 12% and cT3 was 88% which indicates that our cohort of patients had a more advanced cT stage compared to most of the patients in the studies discussed here.

When we see the pre-treatment clinical nodal category, 56.8% of our patients had cN2 and 30% had cN1 disease. This is close to comparison with the RAPIDO study in which 65% of patients had cN2 and 27% had cN1 disease. The MSKCC study also

had relatively high percentage of patients with a higher cN disease (43% cN2, 49% cN1). The PRODIGUE-23 trial had a bit different nodal category distribution; 65% had cN1 and cN2 in 25% of the patients. In the Egyptian study 20% of patients had cN2 disease, 33.3% had cN1 and 46.7% had cN0 disease.

The MRF is involved by the tumor in 86.5% of our patients; this figure is 62% in RAPIDO and only 22% in the PRODIGUE-23 trial. Despite some variations, our patients share a common group of risk stratification with those patients enrolled in the above-mentioned studies. They all have a common feature: “pelvic MRI defined high risk features” which is a recently coined term to describe patients with large/bulky primary tumors, a threatened or involved MRF or a large number of lymph nodes who are thought to be at increased risk of metastatic disease. (25,26,28,29,30)

Majority of the patients in this retrospective study were treated with the TNT approach; an approach which is now accepted as a standard treatment for patients with high risk locally advanced rectal cancer. Some of our patients were treated with LCCRT and no induction chemotherapy. Though we have been using the combination of these two approaches for the past many years in our institution, the efficacy of our neoadjuvant treatment strategy is not studied and hence unknown. Addressing this issue is the main aim of this study. In this manuscript we report the initial efficacy results of our experience with these combined approaches.

In the standard trials conducted on TNT the sequence of neoadjuvant therapy is such that either SCRT or LCCRT is given first and then followed by consolidation chemotherapy before TME. Our sequencing of the neoadjuvant therapy modalities is somehow different from the approach used in the standard trials. We used induction FOLFOX4 or CAPEOX followed by LCCRT and then TME surgery for those who were able to achieve a conversion to resectability. This is similar to a retrospective study done at MSKCC: 57 patients received induction chemotherapy in the form of FOLFOX (median 7 cycles) then CRT.

The radiotherapy technique used to treat our patients was predominantly conventional 2D RT (65%), which is in sharp contrast to all of the studies discussed here which used either 3DCRT or IMRT.

The overall treatment time in patients who took LCCRT or LCRT ranges from 5 weeks to 12 weeks, and the mean was 6.9 ± 1.4 weeks, which is abnormally protracted compared to the 5.5 weeks of the standard used by other studies. This may have its own effect on the treatment outcomes.

The time gap from the completion of radiotherapy to clinical response evaluation was 8.8 ± 7.2 weeks, compared to 4 weeks in a study done at Alexandria University study, and 6-8 weeks in a study conducted on 35 patients at Istanbul university to determine the role of MRI with DWI in re-staging rectal cancer after neoadjuvant chemoradiotherapy.

When we see the rate of clinical response rate, 15 patients (40.6 %) had tumor down staging (this down staging lead to a clinical conversion to resectability only in 12 patients, 3 patients had a down staging from cN+ to cN0 with no change in cT stage or CRM status, which was not helpful to define resectability). This is a very low response rate compared to the Alexandria University study which was 76.7%. One patient had complete clinical response (2.7%) compared to 9 (15.8%) in the MSKCC study and 8.5% in the Istanbul University study. (31) Twenty patients (54%) had stable disease and 2 patients had progressive disease.

Regarding CRM status, 10 patients (31.2% of all the patients who had positive CRM before neoadjuvant therapy) who initially had involved CRM achieved free CRM after neoadjuvnat therapy. This figure was 37.5 % in the Istanbul University study, where 3 of the 8 the CRM positive patients became CRM free after neoadjuvant chemo-radiotherapy.

The time gap between completion of neoadjuvant CRT and surgery ranged from 10 weeks to 58 weeks, the mean being 18 ± 14.4 weeks. This is in great disparity with the 6 - 8 weeks in the MSKCC and the Alexandria University study; 7 weeks in the Polish-II & PRODIGUE-23 studies, 8 ± 2 weeks in the LCCRT arm of the RAPIDO trial.

The resectability rate in our patients after neoadjuvant therapy was limited to 30% which is a very low value compared to the Polish-II study (81%), MSKCC (94%), PRODIGUE-23 (92%), RAPIDO (89%) and the Egyptian study (100%). Sphincter preservation was possible only in 2 of the 11 patients who undergo surgery (18.2%), compared to 59% in the Polish-II, 85% in PRODIGUE-23 and 76.6% in the Egyptian study mentioned above. R0 resection was achieved in 7 out of 11 of our patients (63%); 71% in the Polish-II, 90% in RAPIDO, 95% in PRODIGUE-23 and 100% in the MSKCC.

No complete pathologic response rate was seen in our patients compared to 3.3 % in the 27% in the MSKCC, 12 % in the Polish-II, 28.4% in RAPIDO and 27.5% in PRODIGUE-23 study. Seven out of 10 patients (70%) who undergone surgical

resection had pathologic down-staging or partial response compared to 73.3 % in the Alexandria University study. (25,26,28,29,30,31)

Table 6: Comparison of the pre-neoadjuvant radiologic staging and pathologic stage in patients who had surgical resection

Patients	Baseline cTN stage	Baseline CRM status	Pathologic TN stage	Pathologic CRM status
1.	T3N0	Free	T3Nx	Unknown
2.	T4aN2	Involved	T2N0	Free
3.	T3N2	Involved	T2Nx	Free
4.	T4aN2	Involved	T2N2a	Free
5.	T4bN2	Involved	T2Nx	Free
6.	T3N2	Free	T3N0	Free
7.	T3N1	Involved	T4aN0	Unknown
8.	T3N2	Involved	T3Nx	Free
9.	T3N2	Involved	T3Nx	Involved
10.	T3N2	Involved	T3N1	Free

Chapter Seven. Strength and Limitations of the Study

7.1 Strength

- ✓ This study was done at the leading oncology center of the country where the highest numbers of oncologic patients are evaluated and treated.
- ✓ MDT clinic discussions and decisions were used as inputs, which clears ambiguity in the staging and treatment options of most of the patients included in his study.

7.2 Limitations and Challenges

- ✓ Incomplete medical data records leading to the small sample size.
- ✓ Some important information in patients' clinical records were missing due to improper handling of patient charts and other medical records. For example, the radiotherapy treatment plan sheets were lost in 6 patients.
- ✓ Most part of the radiotherapy logbook for the year 2011 E.C is missing and hence patients who received their treatment in that period of time were not included in the study.

Chapter Eight. Conclusion

Most if not all of the patients that we give neoadjuvant chemoradiotherapy at TASH have a very advanced disease with only a little hope of surgical resectability even after completion of neoadjuvant therapy. This could inform the possibility that we are giving the neoadjuvant therapy for patients who may not benefit from getting it.

The overall treatment time of chemoradiation in our institution is a protracted one. This may be due to frequent radiotherapy machine breakdown and failure to maintain it on time which leads to treatment interruption in many patients. This may have a negative impact on the treatment outcomes.

This study revealed that the time gap between completion of chemoradiotherapy and surgical resection or EUA (to check the possibility of surgical resection) is very long. It is known that any time duration longer than 10 weeks after completion of CRT decreases the likely hood of resect-ability. It is one of the main reasons why our patients had a poor resectability and clinical/pathologic response rate. Incomplete pathologic reporting is common in our study which needs to be improved.

Sphincter preservation rate is very low and this may by due to high number of patients with low rectal cancer in this study.

Chapter Nine. Recommendations

- ✓ It is better to improve patient selection for NACT, and follow recommended time gap to surgery
- ✓ Need to improve patient follow up and medical data recording and keeping
- ✓ Better to follow a standard tool for post-neoadjuvant therapy response clinical/response evaluation.
- ✓ Pathology reporting scheme need to be improved.

Chapter Ten. References

1. Cancer 3. 2021;(March):1–6., WHO 2021 caner fact sheets .
2. Copur MS, Wedel W, Jonglertham P, Zusag T, Horn A. Locally advanced ectal cancer: What is the standard of care? Oncol (United States). 2020;34(1):1–10.
3. Papaccio F, Roselló S, Huerta M, Gambardella V, Tarazona N, Fleitas T, et al. Neoadjuvant chemotherapy in locally advanced rectal cancer. Cancers (Basel). 2020;12(12):1–12.
4. Bray F, Jemal A, Torre LA, Forman D, Vineis P. Long-term Realism and Cost-effectiveness: Primary Prevention in Combatting Cancer and Associated Inequalities Worldwide. J Natl Cancer Inst. 2015;107(12):djv273.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. 2021;71(3):209–49.
6. Cancer N, Plan C. FEDERAL MINISTRY OF HEALTH. 2020;(October 2015).
7. Tigeneh W, Molla A, Abreha A. Pattern of Cancer in Tikur Anbessa Specialized Hospital Oncology Center in Ethiopia from. 2015;1–5.
8. Graham A, Adeloye D, Grant L, Theodoratou E, Campbell H. Estimating the incidence of colorectal cancer in Sub-Saharan Africa: A systematic analysis. J Glob Health. 2012;2(2).
9. Memirie ST, Habtemariam MK, Asefa M, Deressa BT, Abayneh G, Tsegaye B, et al. Estimates of cancer incidence in Ethiopia in 2015 using population-based registry data. J Glob Oncol. 2018;2018(4).
10. Feuchtner J, Mathewos A, Solomon A, Timotewos G, Aynalem A, Wondemagegnehu T, et al. Addis Ababa population-based pattern of cancer therapy, Ethiopia. PLoS One. 2019;14(9):1–12.
11. Country-specific I, Ababa A, Cancer C, Method R, Country-specific M, Computed P, et al. 114 963 583. 2020;133:1–2.
12. Irabor DO, Afuwape OO, Ayandipo OO. The Present Status of the Management of Colon and Rectal Cancer in Nigeria. J Cancer Res. 2014;2014:1–7.

13. Salem ME, Hartley M, Unger K, Marshall JL. Neoadjuvant combined-modality therapy for locally advanced rectal cancer and its future direction. Oncol (United States). 2016;30(6).
14. Sharma A, Alatise OI, Adisa AO, Arowolo OA, Olasehinde O, Famurewa OC, et al. HHS Public Access. 2021;
15. Gastroenterol WJ. Contents. 2019;9327(33).
16. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926–33.
17. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. N Engl J Med. 2004;351(17):1731–40.
18. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27(31):5124–30.
19. Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: A randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol. 2012;13(6):579–88.
20. O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: Surgical end points from national surgical adjuvant breast and bowel project trial R-04. J Clin Oncol. 2014;32(18):1927–34.
21. Roeder F, Meldolesi E, Gerum S, Valentini V, Rödel C. Recent advances in (chemo-)radiation therapy for rectal cancer: a comprehensive review. Radiat Oncol [Internet]. 2020;15(1):1–21. Available from: https://doi.org/10.1186/s13014-020-01695-0
22. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93(10):1215–23.
23. Zaborowski A, Stakelum A, Winter DC. Systematic review of outcomes after

total neoadjuvant therapy for locally advanced rectal cancer. Br J Surg. 2019;106(8):979–87.

24. Borg C, Rullier E, Marchal F, Etienne P-L, Rio E, Francois E, et al. LBA21 Neoadjuvant mFOLFIRINOX and preoperative chemoradiation (CRT) versus preoperative CRT in patients with T3-4 rectal cancer: Surgical and quality of life results of PRODIGE 23 phase III trial. Ann Oncol [Internet]. 2020;31:S1152. Available from: https://doi.org/10.1016/j.annonc.2020.08.2249
25. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EMK, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):29–42.
26. Ciseł B, Pietrzak L, Michalski W, Wyrwicz L, Rutkowski A, Kosakowska E, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: Long-term results of the randomized Polish II study. Ann Oncol. 2019;30(8):1298–303.
27. Bazan JG, Koong AC, Chang DT. Rectal cancer. Med Radiol. 2015;67:303–14.
28. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(5):702–15.
29. Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. JNCCN J Natl Compr Cancer Netw. 2014;12(4):513–9.
30. Elmessiry M, Abouelnagah G, Elzeiny M, Gebaly A, Awad A, Attia G, et al. Predictors of tumor response to neoadjuvant chemoradiation in locally advanced rectal cancer Egyptian patients. Arch Clin Exp Surg. 2015;4(1):21.
31. Bayram I, Bakir B, Kartal MGD, Kunduz E, Bayram O, Turkay R, et al. The role of MRI with diffusion-weighted imaging in restaging rectal cancers after neoadjuvant chemoradiotherapy. South African J Radiol. 2016;20(1):1–6.

Chapter Eleven: Annex

Annex 1: Data Extraction Tool utilized in the study

Serial No.	Variables	Category	
1.	MRN	_____	
2.	Age of the patient	_____	
3.	Sex of the patient	a. Female b. Male	
4.	Baseline/ pre-neoadjuvant therapy workup and/or staging procedure used.	a. Serum CEA b. Colonoscopy c. Pelvic MRI d. Abdominopelvic CT scan e. Abdominal U/S f. CXR g. Chest CT scan h. Exploratory laparotomy	
5.	Colonoscopic Biopsy	_____	
6.	Tumor grade/ degree of differentiation	_____	
7.	Baseline clinical/ radiologic TNM stage	**T stage**	a. T1 b. T2 c. T3 d. T4a e. T4b
		N stage	a. N0 b. N1 c. N2 d. Nx
8.	Location of the tumor in the rectum	a. Upper rectal b. Mid-rectal **c.** Low rectal **d.** Involved multiple regions	
9.	Circumferential radial margin status on baseline pelvic imaging	a. Free b. Threatened **c.** Involved **d.** Unknown	
10.	Pelvic organs involved by the tumor (pre-neoadjuvant therapy)	_____ _____	
11.	Neoadjuvant therapy the patient took	a. LCCRT b. SCRT c. Induction chemotherapy followed by LCRT d. LCRT only	
12.	Type of chemotherapy used	_____	

	concurrently with RT		
13.	Induction chemotherapy regimen used (if used)	_____	
14.	Radiotherapy technique used	a. Conventional/2D RT b. V-sim/3D RT c. 3DCRT	
15.	Radiotherapy dose given and fractionation	_____ _____	
16.	Overall treatment time of RT	_____	
17.	The time gap between completion of RT and treatment response evaluation by imaging	_____ _____ _____	
18.	Pelvic imaging modality used for treatment response evaluation	a. Pelvic MRI b. Pelvic CT scan	
19.	Metastatic workup	a. Abdominal CT scan b. Chest CT scan c. Abdominal U/S d. Chest X - ray	
20.	Post neoadjuvant therapy radiologic response evaluation (yTNM)	yT stage	a. T0 b. T1 c. T2 d. T3 e. T4a f. T4b
		yN stage	a. N0 b. N1 c. N2 d. Nx
		M stage	a. No metastasis b. Evident metastasis
21.	Post neoadjuvant therapy CRM status on pelvic imaging	a. Involved b. Threatened c. Free d. Unknown	
22.	Pelvic structures involved by the tumor up on radiologic response evaluation	_____ _____	
23.	Post neo-adjuvant therapy serum CEA level	_____	
24.	Curative surgical resection	a. Yes done b. Not done	
25.	Type of surgery done (if surgery is done)	a. APR b. LAR	
26.	The time gap from completion of neoadjuvant	_____ _____	

	CRT to surgical resection		
27.	The reason why curative surgical resection was not done. (if is surgery not done)	_____ _____	
28.	Postoperative pathology report	ypT stage	a. T0 b. T1 c. T2 d. T3 e. T4
		ypN Stage	a. N0 b. N1 c. N2 d. Nx
		Proximal surgical margin	a. Positive b. Negative c. Unknown
		Distal surgical margin	a. Positive b. Negative c. Unknown
		CRM	a. Positive b. Negative c. Unknown