

6 Treatment Pattern and Outcome of Locally Advanced Rectal Cancer in Resource-Constrained Countries: Experience at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

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ABSTRACT

PURPOSE Management of locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision. Recently, total neoadjuvant treatment (TNT) has gained attention. In developing countries, patients with rectal cancer often present at advanced stages. This study assesses treatment patterns and outcomes in LARC at a largest referral center in Ethiopia.

MATERIALS AND METHODS A cross-sectional study was conducted on 100 patients with LARC treated at Tikur Anbessa Specialized Hospital from January 2020 to September 2022.

RESULTS The median age at diagnosis was 45.5 years (range, 20–86), with 51% male. Of the patients, 81% had no previous oncologic treatment and 75.3% was discussed in a multidisciplinary tumor board. Up-front surgery was planned for 44.4% of patients, whereas 22.2% and 8.6% were assigned to TNT and NACRT, respectively. Among 81 treatment-naïve patients, 79 were triaged for surgery, but only 47 (59.5%) underwent surgery, achieving an 89.9% R0 resection rate. Of 36 up-front planned surgeries, 35 proceeded as planned, whereas only 12 of 43 (28%) planned after neoadjuvant treatment underwent surgery. Neoadjuvant chemotherapy (NACT) was given to 37% of patients, with 16.7% (5 of 30) undergoing subsequent surgery. Radiotherapy was given to 24.2% of participants, with 56.25% undergoing surgery. Short-course radiotherapy (SCRT) was given to two patients. Only 14.8% completed all planned treatments, with radiation waiting time (median, 10 months) being the main impediment.

CONCLUSION Timely administration of neoadjuvant treatment is not possible in most resource-limited settings. Because of better treatment completion, up-front surgery looks a more viable option than NACT in these situations. Extended waiting time for radiotherapy can be mitigated by opting for alternatives like SCRT in selected patients.

ACCOMPANYING CONTENT

 [Data Supplement](#)

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INTRODUCTION

Cancer is one of the leading causes of death worldwide. The burden is expected to rise because of population growth, aging, and an increase in the prevalence of risk factors. Colorectal cancer (CRC) is the second most common cause of death and the third most common cancer, according to the 2020 Global Cancer Observatory report. The disease continues to be a serious health issue in emerging nations.^{1,2}

In Ethiopia, CRC is the most common cancer in men and the fourth most common in women, with the majority diagnosed

at advanced stages. In one study, despite a high percentage of patients being recommended for neoadjuvant chemoradiotherapy, only few get it because of long waiting lists. As a result, many patients end up undergoing immediate surgery or wait for months before receiving radiotherapy. Another study reported that only 7.2% of patients are able to receive radiotherapy, leading to a poor 1-year survival of 63.1%.^{3–6}

The management of rectal cancer, especially when presenting as locally advanced, should be conducted through a multidisciplinary team (MDT). The CRC MDT serves as a platform for coordinating, communicating, and making

CONTEXT

Key Objective

In resource-limited setups, what is the pattern of treatment and outcome of locally advanced rectal cancer (LARC)?

Knowledge Generated

A heterogeneous pattern of treatment was seen. Because of the long waiting time for radiotherapy, few numbers of patients were able to get radiotherapy. Thus, only 14.8% of patients completed all their treatment. Most patients were managed with up-front surgery with an 89.9% R0 resection rate. Of patients who took neoadjuvant chemotherapy, only 16.7% had undergone subsequent surgery. Short-course radiotherapy (SCRT) was used in a few patients.

Relevance

This study identifies major gaps in the management of LARC in Ethiopia. The availability of radiotherapy is a major limiting factor, and alternative modalities like SCRT should be sought for some. If neoadjuvant treatment is not feasible, up-front surgery looks better considering treatment compliance.

decisions among professionals in radiology, pathology, surgery, medical, and radiation oncology, alongside nurse specialists and coordinators. Multidisciplinary discussions may influence the management and outcome of patients with locally advanced rectal cancer (LARC).^{5,7-11}

Although patients with early-stage rectal cancer can be treated with up-front surgery, the National Comprehensive Cancer Network (NCCN) and its harmonized version recommend initial neoadjuvant therapy to downstage the tumor and allow for an adequate surgical excision. Patients who undergo up-front surgery and receive adjuvant treatment might have equal survival as those who took neoadjuvant treatment, but they have a considerable risk of positive margin, local recurrence, and acute toxicity.¹²⁻¹⁵

For patients with LARC, neoadjuvant treatment options include long-course chemoradiotherapy (CRT) and short-course radiotherapy (SCRT). Studies comparing the two modalities have revealed comparable results. As a neoadjuvant alternative for more advanced stages, total neoadjuvant treatment (TNT) which combines induction or consolidation chemotherapy with short- or long-term radiation has been studied in recent years and proved to be effective. Despite being evaluated in several studies and showing some benefit in some groups of patients with LARC, neoadjuvant chemotherapy (NACT) alone has not been incorporated into most of the standard treatment guidelines yet.¹⁵⁻²³

Furthermore, when resources are limited, SCRT has significant advantages over standard long-course CRT. During the COVID-19 pandemic, for example, SCRT reduced hospital stays and the risk of virus infection for patients and staff.^{24,25} It allowed for early initiation of systemic chemotherapy, which might decrease distant metastasis²⁶ and the risk of acute toxicity when compared with long-course CRT.²⁷ As a result, SCRT may be more practical without compromising

efficacy for treating resectable rectal cancer in resource-constrained settings.

Although NACRT is still the recommended treatment for patients with LARC, it may not be practical for patients in less developed nations because of the lack of resources. As the only radiotherapy facility for a population of more than 100 million, many of our patients are unable to receive standard radiotherapy promptly and are forced to resort to alternative regimens, including up-front surgery and NACT, instead of the accepted standard of care.

We planned to assess our experience, which might give insight into how patients in a developing country are treated, and see how resource limitations affect treatment choices and impact outcomes.

MATERIALS AND METHODS

Study Design and Patients

Despite Ethiopia's population exceeding 120 million, the country has few cancer centers and four centers equipped with a functional linear accelerator that offers radiotherapy. This study took place at Tikur Anbessa Specialized Hospital (TASH), a tertiary-level hospital in Addis Ababa. TASH is the main cancer diagnostic and treatment facility, serving as the only center in the capital with radiotherapy. The remaining three radiotherapy centers are located in other regions of the country.

A single-institution cross-sectional study enrolling patients treated from January 1, 2020, to September 2022 was conducted. Data were extracted from medical records using data extraction forms. All patients 18 years and older with histologically confirmed rectal adenocarcinoma and locally advanced stage (American Joint Committee on Cancer Tumor stage T3 or T4, nodal stage N1 or N2, and tumors involving

mesorectal fascia (MRF)) were included. Patients with incomplete medical records and/or who received more than two different modalities of therapy at other centers were excluded.

Patients deemed eligible had comprehensive history, physical examination, and biopsy during colonoscopy or emergency surgery for diversion stoma in patients of obstructive symptoms. Pelvic magnetic resonance imaging or abdominopelvic computed tomography (CT) scans were used to assess primary tumor staging. Metastatic evaluation was conducted using abdominopelvic sonography and chest x-ray, with suspicious or indeterminate lesions followed up with CT scans. Complete blood cell count and renal and liver function tests were available before active treatment.

Final staging for treatment decision was based on surgical pathology when available and clinical and imaging findings in patients where the tissue specimen was insufficient/unavailable. Our center does not have an institutional protocol for rectal cancer management, and the NCCN, Radiation Therapy Oncology Group (RTOG), and American Society for Therapeutic Radiology and Oncology (ASTRO) guidelines were followed for stage-based delivery of treatment.^{15,28,29}

All patients who underwent radiotherapy had CT simulation with intravenous (IV) and per os contrast, and images were taken with a 0.5-cm slice thickness for treatment planning. Gross tumor volume, clinical target volume, planning target volume, and organ at risk delineation were performed according to international consensus guidelines.^{28,29} Three-dimensional conformal radiation (3DCRT) planning was used for all patients, with prescriptions for 54 Gy in 27 fractions for long-course treatment and 25 Gy in five fractions for SCRT. In patients taking long-course treatment, concurrent capecitabine with a dose of 850 mg/m² orally twice a day was given during the days of radiotherapy.

Operational Definitions

Radiotherapy waiting period is the time in months from the initial decision for radiotherapy (as determined by MDT meetings or outpatient oncology visit) to actual initiation of treatment or the date of data collection for those still awaiting treatment. Surgical waiting time is the time in days from treatment decision to surgery.

Data Collection and Statistical Analysis

Data were gathered and analyzed using IBM SPSS v26. The chi-squared test and Fisher's exact test were used to identify associations between dependent and independent categorical variables, with $P < .05$ signifying statistical significance.

Ethical Considerations

The study was conducted following Addis Ababa University's ethical guidelines after securing approval from the

Department of Clinical Oncology Research Committee. Data were used solely for this study, and privacy was maintained by omitting personally identifiable information.

RESULTS

Sociodemographic and Clinical Characteristics

There were 198 patients of LARC during the study period. Ninety-eight patients were excluded because of factors such as inadequate investigations, multiple previous treatments, nonadenocarcinoma histology, ambiguous diagnosis, and poor performance status for whom only supportive care was recommended.

Among 100 patients who met the study's inclusion criteria, 51% was male (Table 1). Fifty-two percent came from outside of the study area (Addis Ababa). The most common histology was adenocarcinoma not otherwise specified (85%), and signet ring histology was reported in six patients all younger than 50 years.

Treatment Decisions and Patterns

Of 100 patients with LARC, 81 presented directly at TASH. The remaining 19 were referred after receiving cancer-directed therapy, 16 of whom underwent surgery and three received chemotherapy.

Among the treatment-naïve patients ($n = 81$), 36 (44.4%) patients were planned for up-front surgery, 18 (22.2%) were planned for TNT, 18 (22.2%) were planned for NACT, seven (8.6%) were planned for NACRT, and two were planned for induction chemotherapy followed by definitive CRT. Sixty-one of 81 (75.3%) were presented at MDT meetings, and the recommendations included up-front surgery, TNT, NACT, and NACRT in 44.3%, 22.9%, 21.3%, and 9.8% of patients, respectively.

Of the seven patients in the NACRT arm, four were planned to have adjuvant chemotherapy, whereas the remaining three were planned to have surveillance. The most common adjuvant treatment ordered for patients managed with up-front surgery was initial chemotherapy followed by subsequent radiotherapy, 33 of 36 (91.7%; Data Supplement, Table S1).

Treatment decisions on the basis of tumor location and staging: up-front surgery was planned in 62.5% of the rectosigmoid and upper rectal tumors, and 44.6% in mid-, lower-, and anorectal regions. NACRT was ordered only for mid-, lower-, and anorectal tumors.

Treatment decisions on the basis of age category: up-front surgery, NACT, TNT, and NACRT were received in 41.3%, 28%, 2.2%, and 6.5% of patients younger than 50 years, respectively, and one patient received induction CT followed by definitive CRT. In the elderly (>70 years), the most common initial treatment modality was NACRT in 37.5% (3

TABLE 1. Clinical Characteristics of All Patients (N = 100)

Variable	Frequency (%)
Age, years, median (range)	45.5 (20-86)
Age categories, years, No.	
<50	57 (57)
50-69	34 (34)
≥70	9
Sex (male), No.	51 (51)
Presentation (symptoms), No.	
Rectal bleeding	82 (82)
Bowel habit changes	60 (60)
Tenesmus	53 (53)
Abdominal pain	33 (33)
Incontinence	3 (3)
Other symptoms	8 (8)
ECOG performance status, No.	
0	6 (6)
I	85 (85)
II	9 (9)
CEA-positive patients ^a (n = 33), median (range)	14.2 ng/mL (5.8-499)
MRI location (tumor epicenter), No.	
Rectosigmoid	13 (13)
Upper rectum	11 (11)
Mid rectum	12 (12)
Lower rectum	54 (54)
Anorectal	10 (10)
MRF invasion, No.	
Yes	53 (53)
No	47 (47)
TNM staging, No.	
T3N0	9 (9)
T3N1	53 (53)
T4N0	12 (12)
T4N1/2	26 (26)
Histologic subtypes, No.	
Adenocarcinoma NOS	85 (85)
Mucinous	9 (9)
Signet ring	6 (6)

Abbreviations: CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; MRF, mesorectal fascia (or invasion of levator ani or sphincter for low rectal tumors); MRI, magnetic resonance imaging; NOS, not otherwise specified.

^aThe cutoff value for positive CEA was taken to be 5.6 ng/mL.³⁰

of 8 patients). There was a significant association between age category and initial treatment choice ($P = .041$; Data Supplement, Fig S1).

Treatments Given and Immediate Outcome

A total of 72 of 81 (88.9%) treatment-naïve patients received their planned first treatment. Among patients who were discussed at MDT meetings, 55 of 61 (90.1%) patients received

their planned first treatment. Considering all planned treatment modalities for each patient, only 12 of 81 (14.8%) completed their intended treatment. The majority, 69 of 81 (85.2%), did not finish their planned treatment because of various reasons, including radiation waiting time (32 of 69, 46.4%), progression during treatment (17 of 69, 24.6%), lost before treatment completion (7 of 69, 10.2%), and disease progression while waiting for treatment (4 of 69, 5.8%). Among the 4 patients who progressed while waiting for treatment, three were waiting for radiotherapy and 1 was waiting for surgery (Data Supplement, Table S2).

A total of 10 of 61 (16.4%) MDT-presented patients were able to finish all planned treatments, whereas 2 of 20 (10%) patients that did not present to the MDT finished their treatment. In terms of treatment delivery, 81 of the 100 patients were referred directly to TASH without any oncologic treatment and were thus evaluated for all possible treatment strategies: surgery, chemotherapy, and radiotherapy, whereas 19 patients had previously received treatment, either surgery or chemotherapy, and thus, only radiotherapy was planned as strategy in these patients. As a result, 81 patients were evaluated for surgery and chemotherapy, whereas all 100 patients were evaluated for radiotherapy. Since our center does not have an institutional protocol for rectal cancer management, we follow NCCN, RTOG, and ASTRO guidelines for stage-based delivery of treatments.

Surgical Outcome

Among treatment-naïve patients, 79 of 81 (97.5%) were planned to undergo surgery: 36 up-front and 43 after neoadjuvant treatment. From these, only 47 of 79 patients (60%) proceeded to surgery. Among the up-front planned surgeries, 35 of 36 (97%) proceeded with the planned surgery, whereas only 12 of 43 (28%) of those planned after neoadjuvant treatment underwent surgery subsequently. Clinical complete response (CCR) and pathologic complete response (pCR) were found in only one patient each, both patients were given NACRT, and 43 of 47 surgeries were elective: 29 (62%) patients were abdominoperineal resection and the remaining were low-anterior resection. Among patients who had up-front surgery, 22 (62.9%) had T3 stage and 13 (37.1%) had T4 stages (Data Supplement, Table S3). The median surgery waiting time with up-front surgery was 30 days (IQR, 26–43 days).

Postoperative margin status was reported in 45 of 47 patients. The margin negative resection rate (R0 resection) was 42 of 47 (89%), with positive circumferential radial margin (CRM) found in five patients, and no clear factor was identified for different margin status (Table 2).

Chemotherapy Outcome

Of 81 treatment-naïve patients, 75 were planned to receive chemotherapy, and 73 of those received it as scheduled.

TABLE 2. Factors Affecting Postoperative Margin Status in Patients Who Have Undergone Surgery

Variable	Factor	Postoperative Margin Status		P
		Positive (n = 5)	Negative (n = 42)	
Surgery timing	Elective	4	40	.29
	Emergency	1	2	
Treatment decided by	MDT	5	31	.32
	Not MDT	0	11	
Surgery order	Up-front	3	32	.59
	After NA treatment	2	10	
Treatment given	NACRT	0	4	.19
	NACT	1	4	
	TNT	1	1	
	Up-front surgery	3	33	
Tumor location	RS and upper rectal	2	9	.58
	Mid-, low-, anorectal	3	33	
TNM group	T3NO	1	2	.45
	T3N+ve	3	24	
	T4Nany	1	16	
Histologic subtype	ADC NOS	5	34	.37
	Mucinous	0	6	
	Signet ring	0	2	
Histologic grade for ADC NOS	Well differentiated	2	22	.02
	Moderately	1	9	
	Poorly	2	0	
	Not reported	0	11	

Abbreviations: ADC, adenocarcinoma; MDT, multidisciplinary team; NA, not available; NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; NOS, not otherwise specified; RS, rectosigmoid; TNT, total neoadjuvant treatment.

Chemotherapy was administered as follows: adjuvant (37 of 73), neoadjuvant (18 of 73), and as part of TNT (18 of 73). Of the 18 patients who initiated chemotherapy as part of TNT, 12 (66.7%) ended up only receiving the chemotherapy component.

Thirty patients underwent NACT as a standalone treatment (n = 18) or as part of TNT but ended up being NACT (n = 12). Among patients who had NACT, 20 of 30 (66.7%) had MRF involvement and 18 of 30 (60%) patients had T4 disease (Data Supplement, Table S3). The regimens taken under this setting were folinic acid, fluorouracil, and oxaliplatin (20, 66.7%), capecitabine and oxaliplatin (8, 26.7%), and in the remaining (2, 6.6%) single agent capecitabine. Seventy percent (21 of 30) of patients who took NACT completed the entire chemotherapy regimen, and within this subgroup, only 23.8% underwent subsequent surgery. Nine patients who did not complete the intended NACT cycles did not undergo surgery. Overall, considering all patients who received NACT, surgery was performed only in 16.7% (5 of 30) of them. Reasons for not undergoing surgery after or during NACT included disease progression, lost to follow-up, death, and refusing surgery in 14, 6, 3, and 2 patients, respectively.

Of the 37 patients who received adjuvant chemotherapy, 31 (83.8%) completed all prescribed cycles. Adjuvant

chemotherapy commenced within 8 weeks for 54% of the patients, and only three patients experienced disease progression during adjuvant chemotherapy.

Radiotherapy Outcome

Radiotherapy was planned in 99 (99%) of them, and all decisions were made at our institution. The planned radiotherapy included adjuvant, neoadjuvant, part of TNT, and definitive in 71%, 7%, 20%, and 2%, respectively. Twenty-four of 99 (24.2%) were able to get radiotherapy as adjuvant (7 of 24), neoadjuvant (7 of 24), definitive (1 of 24), and TNT (9 of 24).

Preoperative SCRT was given to 12% (2 of 17) of patients who took preoperative radiotherapy, and 88% (15 of 17) received long-course CRT. The most common reason for not getting radiation was waiting time. Twenty-seven patients were still waiting for adjuvant radiotherapy at the time of analysis, and five patients had progressed while waiting. The median (range) radiotherapy waiting time was 10 (1–26) months.

Among the seven patients who took NACRT, four (57.1%) underwent subsequent surgery, with one patient having a pCR. One patient had a CCR on preoperative evaluation, and

surgery was omitted. In those patients who took TNT (nine), five (55.5%) underwent subsequent surgery.

There was no association between postoperative margin status and histology subtype with only one from each receiving radiotherapy, grade ($P = .2$), TNM stage ($P = .1$), MRF involvement ($P = .4$), discussion on MDT ($P = .4$), and getting adjuvant radiotherapy.

DISCUSSION

In this study, we characterize treatment patterns of LARC in one of the largest tertiary centers in Ethiopia that have all treatment modalities including MDT. Most patients were young (median age 46 years and 57% younger than 50 years) and presented at an advanced stage (63% with either T4 or MRF involvement). Our findings are similar to those reported in other studies and contrary to what is seen in developed countries, and further research is needed to determine common reasons for delayed and younger age of presentations.^{4,5,32}

Evidence-based guidelines recommend patients with LARC be treated with a neoadjuvant treatment, which incorporates radio- and chemotherapy followed by surgery.¹⁵ However, in our study, we see that most patients were approached with up-front surgery. This could be due to the long waiting list for radiotherapy with a long median waiting time of 10 months. This problem was also reported previously in another study.³³ A lengthy median radiotherapy waiting period of 12.2 months was also recorded by a Nigerian study.³⁴

Radiotherapy is one of the main treatment modalities for rectal cancer. Heretofore, there was one cobalt-60 machine in Ethiopia for more than 120 million people. Recently, three linear accelerator (LINAC) machines were introduced in TASH, Jimma University Medical Center, Haramaya, and Hawassa University Hospitals, with the ratio of LINAC to population being 1:30 million.³⁵⁻³⁷ The long waiting period for radiation resulted in most receiving alternate treatments rather than the standard neoadjuvant treatment, which incorporates radiotherapy.

One feasible solution for long waiting times with equivalent clinical outcomes is using SCRT, which was recommended by different studies as an alternative treatment modality, especially in resource-limited settings.^{38,39} In our study, only two (12%) patients received preoperative SCRT. Despite the problem of a long waiting list, the reason for not using SCRT is not clear. One possible reason could be the practice of using cobalt machine with a conventional two-dimensional technique, which is associated with more toxicities than the recently practiced 3DCRT, and physicians were not able to easily change to a high dose per fraction of short-duration regimen. Further investigation is needed to understand why SCRT regimen has not been adopted since the LINAC machine's inception 3 years ago.

Few patients in our study underwent TNT. TNT with SCRT or long-course radiotherapy is a comprehensive treatment approach for LARC that has a practical advantage over the existing approach, most importantly in resource-limited settings where early-stage diagnosis and quality care are challenging. TNT could improve the rate of sphincter preservation, decrease the chance of disease progression, enhance patient compliance, and make it easier to identify patients who would benefit from nonoperative therapy. Better MDT coordination and integration further enhance the applicability of TNT, which is essential for LARC's optimal outcomes.^{31,40} As a result, TNT is an essential approach to consider for LARC management in resource-constrained settings.

This study aimed to assess the outcomes of common treatment modalities. One of the benefits of neoadjuvant treatment according to contemporary studies is to increase the R0 resection rate.^{12,14} Despite many patients with a more advanced stage and a significant proportion of those who underwent up-front surgery, the positive CRM rate was 11.1%, which was comparable with a study performed in the United Kingdom reporting a positive CRM rate of 12.5% in patients who were presented on MDT and took neoadjuvant treatment.

NACT is still not incorporated into major standard guidelines for the management of LARC; in our study, 30 patients planned to receive this modality as a first treatment, and their outcomes were not satisfactory. This contrasts with the recently published PROSPECT trial, which reported favorable outcomes in patients who underwent NACT. This could be due to the fact that our patients have a more locally advanced stage and did not get timely therapy.²³

Our study has notable limitations. First, we did not conduct an in-depth analysis of overall survival and progression-free survival because of the short follow-up time. These aspects were extensively covered in a previous report on CRC survival by Zingeta et al,⁶ conducted at the same center. Finally, the single-center nature introduces potential bias, influenced by center-specific factors and patient demographics.

In conclusion, in general, our study revealed nonconformance to standard rectal cancer treatment recommendations, with no specific patterns observed. The major obstacle to adequate management is the lack of adequate radiotherapy services.

Alternative radiotherapy treatment options like SCRT should be used more in these countries to reduce radiotherapy waiting time although this short-course regimen should be studied in a randomized controlled trial with the inclusion of population like ours. If feasible, more patients with LARC should receive standard neoadjuvant treatment with radiotherapy. Alternatively, in resource-constrained countries, up-front surgery followed by adjuvant CRT may be preferable to NACT, as patients receiving NACT seemed to have poor rates of undergoing subsequent surgery.

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DATA SHARING STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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