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Original research article

Role of Preoperative Chemoradiotherapy in Downstaging Locally Advanced Rectal Cancer

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Abstract

Background: Neoadjuvant chemotherapy is frequently used in the treatment of a number of solid tumour malignancies, although its effectiveness in treating locally advanced colorectal cancers is yet unknown. We in the current study tried to assess the complications of neoadjuvant chemoradiotherapy in rectal cancer and to assess response to neoadjuvant chemoradiotherapy.

Methods: All patients with carcinoma rectum who presented to MNJ Institute of Oncology and Regional Cancer Center was evaluated by clinical examination, sigmoidoscopy or colonoscopy, staged by MRI pelvis and CT chest and abdomen. Based on the findings, patients with tumors assessed as locally advanced (T3 and T4, N+) are sent for neoadjuvant therapy with concurrent chemoradiotherapy or radiotherapy. N=72 patients with locally advanced carcinoma rectum were identified for the study and referred for neoadjuvant chemoradiation.

Results: Response to Neoadjuvant chemoradiotherapy (NACRT) N=8 patients had clinically progressed while on neoadjuvant chemoradiotherapy, both locoregionally and also developed systemic metastases. Response assessment was done using MRI before NACRT and before surgery. Patients with locally advanced rectal cancer with involvement of mesorectal fascia or loss of fatty plane with prostate or vagina preoperatively had post-radiotherapy changes suggestive of fibrosis. All the n=54 patients (including those who did not consent to surgery) showed radiological response though downstaging did not occur in all the cases.

Conclusion: In this study, the pathologic complete remission using this combined modality was 4%. The pathologic downstaging effect was 48%, including pathologic complete response. Complications especially when extra levator excision is done and reconstruction is performed are fraught with prolonged morbidity. Neoadjuvant chemoradiotherapy as part of a multimodality treatment strategy for locally advanced rectal cancer is safe with acceptable morbidity. Oncologic outcomes in the form of margins were good.

Keywords: Advanced rectal cancers**,** Downstaging, Neoadjuvant chemoradiotherapy (NACRT).

Introduction

Rectal cancer is traditionally included in colon cancer registries. Worldwide, colorectal cancer is the third most common cancer in both females and males. There is a decline in the incidence and mortality rates of colorectal cancers in the developed world mainly due to early detection and better treatments. [1,2,3] In India, colorectal cancer is the 8th most common in men and 9th among women. The annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively. The AAR for colon cancer in women is 3.9 per 100000. [4] Colon cancer ranks 8th and rectal cancer ranks 9th among men. For women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th. [4] The ICMR reports indicates rising rates of colorectal cancer incidence although still much less than even other Asian countries like China and Japan. [5] Hereditary syndromes such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), and MUTYH-associated polyposis (MAP) are samples of familial colon cancer syndromes. [6] Moreover, patients with a personal history of CRCs or adenomatous polyps of the colon are at risk for the future development of colon cancer. The prevalence of K-Ras mutations and mutation patterns in the p53 gene in rectal cancers are also different from those seen in colon cancers. [7] Age and gender are important risk factors affecting both colon and rectal cancers. A statistically significant increased risk for colon cancer has been reported with increased height. For the Body Mass Index (BMI), there is a different effect on CRCs between men and women. A systematic review has reported that each 5 kg/m^2 increase in BMI is associated with a 24% and 9% increased incidence of CRCs in men and women, respectively. Moreover, there is a meaningful increased risk in the highest category of BMI among women for rectal cancer. [8, 9] Surgery remains the mainstay of treatment. NCCN currently recommends neoadjuvant chemoradiation for all T3 and above or any node-positive rectal cancer patients to receive chemoradiation, either long course or short course. ESMO recommends neoadjuvant chemoradiation for bad and ugly rectal cancers (locally advanced (T3c, T3d) or very low or with extra mucosal vascular invasion or extranodal, clinical N1 and N2 disease or when levators are threatened or when mesorectal fascia is involved). MRI assessment plays a very important role in recommending upfront surgery in both NCCN and ESMO guidelines. [10] Both guidelines stress the importance of CRM in deciding which patients can receive neoadjuvant short course radiation such that T4 tumors receive long course chemoradiation. Watch and wait policy of not operating after chemoradiation, in the event of clinically complete response is an option only in medically inoperable patients while in others it is still investigational. The optimal management of locally advanced rectal adenocarcinoma is thus multimodal. With this background, we in the current study tried to assess the complications of neoadjuvant chemoradiotherapy in rectal cancer and to assess response to neoadjuvant chemoradiotherapy.

Material and Methods

This is a cross-sectional interventional study done at MNJ Institute of Oncology and Regional Cancer Centre, Hyderabad, Telangana, a tertiary referral center for the management of cancer patients in the state. The protocol for the study was approved by the Institutional Ethical committee. Written consent was obtained from all the participants of the study after explaining the nature of the study in the local language.

Inclusion Criteria

1. Histopathology proven adenocarcinoma of the rectum within 12 cm from the anal
2. verge
3. MRI staged tumor T3 orT4 and any lymph node-positive disease.
4. Received neoadjuvant radiation or chemoradiation

Exclusion Criteria

1. Patients were not fit for anesthesia for surgery
2. Metastatic disease

All patients with carcinoma rectum who presented to MNJ Institute of Oncology and Regional Cancer Center was evaluated by clinical examination, sigmoidoscopy or colonoscopy, staged by MRI pelvis and CT chest and abdomen. Based on the findings, patients with tumors assessed as locally advanced (T3 and T4, N+) are sent for neoadjuvant therapy with concurrent chemoradiotherapy or radiotherapy. N=72 patients with locally advanced carcinoma rectum were identified for the study and referred for neoadjuvant chemoradiation. However, n=10 patients were lost to follow-up during or after chemoradiotherapy and couldn't be contacted. n=4 patients denied consent for surgery. n=8 patients progressed locoregionally or had a distant disease and were not taken up for surgery. Radiotherapy is given in fractions of 180-200 Gy 5 days a week for up to 50.4 Gy. Four fields parallel AP-PA fields are used. IMRT is used for dose painting. Radiation therapy fields include the tumor or tumor bed, with a 2–5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes are also included for T4 tumors involving anterior structures.

The radiosensitizing dose regimens used are as follows:

1. Capecitabine 800-1000 mg/m^2 PO twice daily 5 days a week or
2. Infusional 5FU 425 mg/m^2 per day and leucovorin, 20 mg/m^2 per day
3. during weeks 1 and 5 of radiotherapy.

Patients are assessed for the response after 6-8 weeks of the last fraction of radiotherapy by MRI scan of the pelvis and distant disease was evaluated by CT scan of the abdomen and chest. Patients who progressed to develop metastases were excluded. Surgery was planned within 10 weeks of chemoradiation. However, due to caseloads at the institution and patient factors, surgery was delayed by 2-3 months in many patients. However, the study protocol doesn't include a time limit after chemoradiation. Surgery included total mesorectal excision and anterior resection or abdominoperineal excision or pelvic exenteration based on the location of the tumor with a margin of 5cm of mesorectum and tumor-free distal mucosal margin. A covering ileostomy was always used when anterior resection was done. The procedure performed for tumors involving adjacent organs included posterior exenteration and anterior exenteration. Perineal reconstruction in advanced anorectal carcinoma was done with a bilateral gracilis flap. Histopathological examination routinely included grade, depth of tumor penetration, number of lymph nodes evaluated, the status of proximal, distal, circumferential (radial), and mesenteric margins, lymphovascular invasion, and satellite tumor deposits. A positive circumferential resection margin is defined as a tumor or metastatic node </=1mm from the margin. Acellular mucin deposits were not considered a residual tumor. Tumor response to neoadjuvant therapy was reported as modified from Ryan R, et al., [11] 0 - Complete response: No remaining viable cancer cells; 1 – Moderate response: Only small clusters or single cancer cells remaining; 2 - Minimal response: Residual cancer remaining, but with predominant fibrosis; 3 - Poor response: Minimal or no tumor kill; extensive residual cancer. After recovery from the surgery all patients are sent for adjuvant chemotherapy. Patients are kept on regular follow-up by clinical examination, imaging as needed, and screening colonoscopy. Serum CEA is followed if elevated preoperatively. During clinical examination, patients are examined for complications and local recurrence/regional recurrence. The maximum period of follow-up is 24 months and the mean period of follow-up is 12 months.

Results

Number of patients who were assessed as locally advanced based on MRI scan of pelvis and sent to receive chemoradiotherapy are n=72. Out of the n=72 cases n=43(59.7%) were males and n=29(40.3%) were females. N=10 patients were lost to follow-up. Of the n=62 remaining, n=8 patients progressed locoregionally or developed distant metastases such that they weren't taken up for surgery. Four patients did not give consent for surgery. So, n=50 patients were managed surgically. The anatomical distribution of tumors in relation to anal verge is depicted in Figure 1.

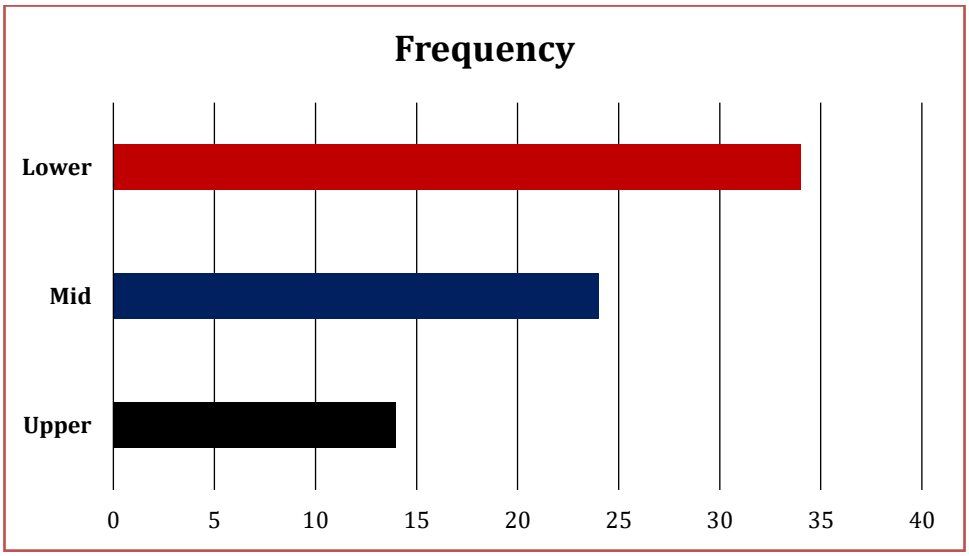

Figure 1: Anatomical distribution of tumors in relation to the anal verge

Out of the n=72 cases in the study most common age group of involvement was between 31 – 40 years with 27.78% of cases followed by 41 – 50 years with 26.4% of total cases. The age-wise distribution of cases included in the study is depicted in table 1.

Table 1: Age-wise distribution of cases in the study

Age group	*Frequency*	*Percentage*
<30	7	9.72
31-40	20	27.78
41-50	19	26.4
>51	26	36.1
Total	72	100

Based on the pre-operative histopathology reports most of the cases in the study 48.61% were having moderately differentiated adenocarcinoma. Poorly differentiated or signet ring cell adenoma was found in 20.83% and well-differentiated adenocarcinoma was the finding in 30.6% of the cases in the study given in table 2.

Table 2: Grade of Malignancy and Histology (based on preoperative histopathology report)

Grade and Histology	*No of Cases*	*Percentage*
Well-differentiated adenocarcinoma	22	30.6
Moderately differentiated adenocarcinoma	35	48.61
poorly differentiated or signet ring cell adenocarcinoma	15	20.83

The type of surgery performed in the cases of the study is depicted in table 3. Operative time in general was longer for patients selected for laparoscopy and those in whom reconstruction was planned. Most of the open surgeries were completed in under 4 hours. Reconstruction significantly prolonged the operative time and also always necessitated elective overnight ventilation of patients. Bleeding more than 600ml occurred in 12 of the patients and correlated with an operative time of more than 300 mins. Cases with excessive (>1000 ml) bleeding were all successfully managed by pressure packing intra-operatively. When the bleeding did not abate packing was done for 24-48 hours and re-exploration was done which always found hemostasis secured.

Table 3: Type of surgery done after neoadjuvant CTRT

Type of surgery	*Frequency*	*Percentage*
Anterior Resection	11	22
Abdominoperineal Excision	34	68
Exenteration (posterior)	5	10
Perineal Reconstruction	3	6
Inoperable	3	6
Lap	9	18
Open	41	82

Complications considered were those that occurred during the admission up to 30 days after surgery. Major medical complications including cardiovascular events occurred leading to death in one patient. Postoperative pulmonary complications including pneumonitis and bronchopneumonia occurred in n=3 patients. The common complication was abdominal wound in n=12 cases. The other complication and percentages are given in table 4.

Table 4: Complications recorded in the cases of the study

Complications	*Frequency*	*Percentage*
Pulmonary complications	3	6
Acute cardiac event	1	2
Perineal Wound dehiscence	8	16
Abdominal Wound Complications	12	24
Ureteric fistula	1	2
Urinary retention	5	10
Gracilis Flap Dehiscence	3	6
Small Bowel Obstruction	2	4
Prolonged Ileus	3	6

Out of the n=50 cases operated n=8 cases developed perineal wound dehiscence which healed in 1-3 weeks either conservatively or by secondary suturing. All three perineal reconstructions are done dehisced and were managed conservatively. One patient developed a ureteric fistula but settled with conservative management. All patients were assessed for post-void residual urine volume before discharge and were continued on catheterization until it was south of 100ml. Post Op HPE (Post CTRT) Average number of nodes harvested was 3. N=23 patients had node-positive specimens. N=22 patients were node negative. Nodal status and tumor status were accurately determined by preoperative MRI in 45 patients (95%). Circumferential resection margins were the most important as proximal and distal margins were always negative.

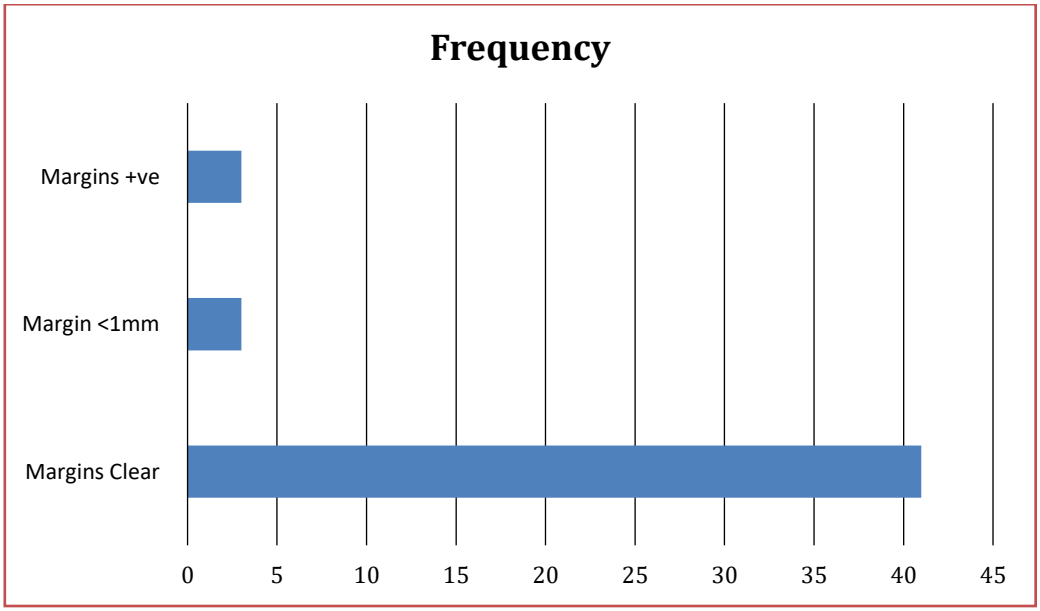

Figure 2: Post Op HPE (CRM) in the cases of the study

Response to Neoadjuvant chemoradiotherapy (NACRT) N=8 patients had clinically progressed while on neoadjuvant chemoradiotherapy, both locoregionally and also developed systemic metastases. Response assessment was done using MRI before NACRT and before surgery. Patients with locally advanced rectal cancer with involvement of mesorectal fascia or loss of fatty plane with prostate or vagina preoperatively had post-radiotherapy changes suggestive of fibrosis. All the n=54 patients (including those who did not consent to surgery) showed radiological response though downstaging did not occur in all. Mesorectal nodes reduced in size or disappeared in n=12 patients and tumor bulk reduced significantly though tumor stage remained the same in n=38 patients, while it was downstaged from T4a to T3 in 12 patients. Of the n=50 patients that underwent surgery, n=3 cases were inoperable. The pathological correlation was also done for the rest of the 47 patients. All but n=2 patients still had a viable tumor in the specimen while only 3 had positive tumor margins. The histopathological assessment revealed, n=16 patients had a moderate response, n=21 had a minimal response, and n=8 had a poor response to neoadjuvant therapy. CEA elevation Only n=9 patients of the n=50 had their CEA levels elevated preoperatively. None of these patients had an inoperable disease. N=7 patients with elevated CEA underwent anterior resection, that is, they had an upper rectal or rectosigmoid disease.

Discussion

N=72 patients diagnosed with locally advanced carcinoma of the rectum were treated at MNJ Institute of Oncology and Regional Cancer Center Department of Surgical Oncology. The population is not representative of other major institutional reviews, perhaps due to the lack of referral programs in this country and the existence of various models of health care delivery systems. Lower socioeconomic and educational status and poor primary care facilities also probably contribute to delayed presentation. The patients were confirmed as having an adenocarcinoma by sigmoidoscopic biopsy. N=5 patients were referred to our institution after undergoing emergency diversion colostomy elsewhere. Further, n=3 patients presented in obstruction to this institution for whom a diversion sigmoid colostomy was already done. In n=4 patients, a diversion colostomy was done for fecal incontinence to prevent perianal sepsis during radiation therapy. Ten patients were lost to follow-up while eight progressed on neoadjuvant chemoradiotherapy. This fact urges us to question whether surgery which is the

definitive management for rectal cancer was unfortunately delayed in these patients. N=4 patients denied consent for surgery despite counseling due to personal constraints, social stigma, and religious beliefs making a permanent stoma unacceptable for them. While n=2 of these have not followed up, n=2 others are still in follow-up with their disease not progressed n=10 months after chemoradiation. The median age was 45 (range 23-70). Males outnumbered females nearly two times. Notably, our patients were younger and more often had poorly differentiated signet ring cell variants. Incidentally reports from tertiary care cancer across the country also report a relatively higher incidence of signet ring cell rectal carcinomas. [11] The majority of the tumors were located in the lower half of the rectum. Most of the patients showed fixation to the rectal wall and/or invasion of the surrounding pelvic organs. Bulky and/or tethered tumors were staged by pelvic MRI as T_3 to T_4 and showed enlarged lymph nodes (marginally or unresectable rectal cancer by digital rectal examination). All patients were evaluated with a CT scan for evaluation of distant metastasis PET scan was not used. Patient and tumor characteristics as compared to the other studies study.

Table 5: Comparison of the present study parameter with other studies

Parameter	Present study	Mark et al., [13]	Park et al. [14]	Marijnen et al., [15]	Sauer et al., [16]
Mean Age	45	59	57	64	62
Range	23-70	28-81	48-66	37-83	30-76
gender ratio	1.5: 1	2: 1	1.7: 1	1.4: 1	2.4: 1
Upper, (8-12 cm)	14 (50)	Mean location 6 cm	42(725)	83 (147)	47 (405)
Middle Rectal (4-8 cm)	24 (50)	not provided	300 (725)	46 (147)	166(405)
Lower Rectal, (< 4 cm)	34 (50)	not provided	360 (725)	83 (147)	157(405)
Poorly Differentiated or signet ring variant	15 (~21%)	-	83 (11%)	-	-

The neoadjuvant chemoradiotherapy protocol used in this study is comparable to other studies. All used a three or four-field box technique, avoiding small bowel. Only a single drug was used in all the patients. Some researchers have routinely included oxaliplatin in the concurrent treatment protocols to maximize radiosensitization.

Table 6: Comparison of Neoadjuvant chemoradiotherapy used with other studies

	Present study	Mark et al., [13]	Park et al., [14]	Marijnen et al., [15]	Sauer et al., [16]
Chemotherapy	Infusional 5 FU/ Capecitabine	Infusional 5FU	Infusional 5FU / Capecitabine	Capecitabine	infusional 5FU
Radiation (all used at least 6MV photon unit)	45-50.4 Gy (in 25-28# 5 days a week, 180-200 Gy Per fraction)	45-50 Gy (in 25-28# 5 days a week, 180 Gy per fraction)	50.4 Gy (in 28 #, 5 days a week, 180 Gy per fraction)	50 Gy (in 25 #, 5 days of week 200 Gy per fraction)	50.4Gy (in 28#, 5 days of the week, 180 Gy per fraction)

Patients were assessed 6-8 weeks after the last dose of radiation. For various reasons, surgery couldn't be performed at 8 weeks in all the patients. The type of surgery performed was: abdominoperineal resection in n=34 patients (68%), low anterior resection in n=11 patients (22%), total pelvic exenteration in 5 patients (10%) and palliative diversion procedure in n=3 patients. The average blood loss was 400-600 ml. All patients routinely were diverted by a loop ileostomy when anterior resection was done after radiation. Ileostomy closure was done 4 weeks later. As such, ultra-low resections or sphincter-saving procedures for patients with prior involvement were not done on any patient. For clinically and radiologically complete responders watch and wait policy was not employed. Also, local excisions for good responders were not done either. Of the n=15 cases selected for laparoscopic resection, n=9 cases were completed while n=6 patients were converted to open. None of the selected cases for laparoscopy were inoperable. The operative time for this cohort was significantly longer than open resections. Neoadjuvant treatment response in the form of reduced tumor bulk probably benefited the lap cases more for technical reasons of operability. N=8 patients had perineal wound dehiscence (16%) which was conservatively managed by dressings and secondary suturing. One patient developed a ureteric fistula and leak from a perineal wound. Three patients for whom reconstruction was used for perineal defects developed flap dehiscence. Five patients developed high post voiding residual urine volumes (range 100-250 ml) all of whom were conservatively managed with prolonged foley catheterization. Compared to other studies, the leak rates, pelvic abscess rates, and prolonged ileus rates seem to be lower in this study because of the policy of mandatory ileal loop diversion when anterior resection is done. Also, cardiopulmonary complications probably occurred in a lesser number of cases because of the otherwise young healthier patients in our study. Gross and microscopic histopathological evaluations of specimens were done uniformly. The quality of the total mesorectal specimen was first assessed immediately after the surgery by the operating surgeon. Margin free (>1mm away from the tumor) resections without microscopic disease at the radial or pelvic side wall margin were achieved in n=44 (88%) patients. Lymphovascular invasion and perineural invasion were reported when present. However, the importance of these findings which is in predicting local and distant failures was not realized in this study due to the short study period. Pathologic assessment of response was five patients were downstaged to yp N0, and n=22 patients had their tumor downstaged from T4 to ypT3.

The number of lymph nodes evaluated was lower compared to other studies though metastatic nodes were reported when present. Pathologic complete response (PCR) of the primary rectal cancer was observed in n=2 patients. Pathological complete response rates are much lower than in other studies perhaps due to differences in patient-tumor characteristics, treatment protocols, and reporting standards. The pathological response level seemed to have only minimally influenced the tumor stage. As has been suggested in the literature, tumor cells tend to persist in the muscularis layer after neoadjuvant treatments. For patients with anorectal tumor location and locally advanced at presentation, this tumor response grading is inconsequential for management. Oncological outcomes mainly reflected by margins and lymph node involvement is comparable to other studies.

All patients selected for the study also received adjuvant chemotherapy which is the standard followed in most institutions to consolidate the multimodality approach. Because of the short study period, local and distant recurrences weren't available to draw significant inferences. Also, the lack of a control arm does not allow comparisons with other treatment protocols, especially the short course of radiotherapy.

Conclusion

In this study, the pathologic complete remission using this combined modality was 4%. The pathologic downstaging effect was 48%, including pathologic complete response. Complications especially when extra levator excision is done and reconstruction is performed are fraught with prolonged morbidity. While this seems inevitable in some cases, perineal complications without the need for reconstruction are quite acceptable. Neoadjuvant chemoradiotherapy as part of a multimodality treatment strategy for locally advanced rectal cancer is safe with acceptable morbidity. Oncologic outcomes in the form of margins were good. A further methodical follow-up to document local or distant failures is needed. Other protocols for delivery of neoadjuvant treatments need to be explored due to the very long duration of management leading to compliance issues, especially in our population.

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