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Original Research Article

A study of total mesorectal excision for rectal cancer-upfront and after neoadjuvant chemotherapy or chemoradiation

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ABSTRACT

Background: Colorectal cancer is a major cause of morbidity and mortality throughout the world. The incidence of rectal carcinoma is increasing in developing countries. Challenge in preoperative evaluation remains to identify patients who might benefit from neoadjuvant chemotherapy or chemoradiation (NACT/RT). The aim of this study was to study the correlation of final histopathology specimen (pathological tumor regression grade) with preoperative MRI (magnetic resonance tumor regression grade) (mrTRG).
Method: This was a prospective observational analysis with operable rectal cancer of mid or distal rectum who underwent total mesorectal excision either upfront or following CT/RT. Preoperative MRI was done for local staging and also to assess response to neo-adjuvant CT/RT. Histo-pathological specimen was assessed for pathological tumor regression and correlation between mrTRG and pathological tumor regression grading (pTRG) analysed.
Results: Out of 79 patients, 69 patients received NACRT and 10 patients underwent upfront surgery. On bivariate analysis mrTRG and pTRG corresponded in 47 patients whereas in 22 patients it didn't correspond. There was a statistically significant agreement between mrTRG and pTRG (p=0.0491).
Conclusions: mrTRG grading was identified as a reliable predictor of pathological response after neoadjuvant chemoradiotherapy and thus a predictor of completeness of resection. So, efforts should be routinely done to do a mrTRG grading as it not only provides oncological safety but also reduces post operative mortality.

Keywords: Carcinoma, Neoadjuvant chemoradiotherapy, Adenocarcinoma, mrTRG, pTRG

INTRODUCTION

Colorectal cancer is a major cause of morbidity and mortality throughout the world. Worldwide colorectal cancer represents 9.4% of all incident cancer in men and 10.1% in women.[1] It is a common disease in western world with highest incidence in elderly population. The likelihood of colorectal cancer diagnosis increases after the age 40 years, rising sharply after age 50 years.[2,3] The incidence of rectal carcinoma is increasing in developing countries.[4] The incidence of cancer is low in India.

The management of rectal cancer has evolved over time. Preoperative imaging with CT is used to find extra-pelvic metastasis, whereas MRI/EUS is used for evaluating locoregional disease. Approximately 50% of the rectal cancer are diagnosecd at the locally advanced stage, with metastatic spread to the lymph nodes in two third of these cases.[1] Patients having early stage disease are taken up for upfront surgery while latter are subjected to neoadjuvant CRT which is followed by TME as LAR or APR.[5,6] Challenge in preoperative evaluation remains to identify patients who might benefit from NACT/RT. High resolution MRI predicts a surgically clear

circumferential resection margin in rectal cancer and also evaluates good or poor response to neoadjuvant CRT based on quantitative (change in tumor volume) and qualitative(grade of tumor response) MR assessment.[7,8] CRM is regarded as the single most important factor for predicting the risk of local recurrence; both direct tumor extension and presence of lymph nodes within 1mm of the CRM is considered as positive margin. MRI forewarns surgeon about the threatened CRM and hence the need for NACRT.[9-11] Due to high reliability of MRI in response assessment and for predicting a negative CRM, MRI pelvis done before and after neoadjuvant CRT gives information regarding the response of tumor to therapy by comparing them side to side and predict the success of operative procedure. In patients who undergo upfront surgery or who have preoperative CRT, onus of surgical outcome lies on the quality of TME. Quality of TME is assessed by looking at the circumferential resection margin (mesorectal fascia), distal resection margin, proximal resection margin and lymph nodes received from the mesorectum.[12] Postoperatively in the final histopathology specimen response to NACRT is assessed by pTRG. Various grading systems have been proposed for pTRG like Dworak et al, Ryan et al AJCC modified Dworak grading.[13,14] Due to the low incidence of CRC in India, there is paucity of literature regarding assessment of response to NACRT with MRI as well as relationship between pathological quality of TME and preoperative MRI. Ours being a high case load centre with attending about 60-70 cases of carcinoma rectum per year inspite of the overall low incidence in Indian subcontinent, will add to the information about the pathological quality of TME and its association with mrTRG.

METHODS

The design of our study was prospective observational. It was done in dept. of surgical oncology, Mahavir Cancer Sansthan and Research Centre, Patna, Bihar, India. Ethical committee approval was taken prior to the study. Sample size included all consecutive patients of operable mid and lower rectal cancers who underwent upfront TME or following NACRT from March 2017 to May 2019. We excluded patients who had distant metastasis or presenting with obstruction or perforation. After diagnosis preoperative local staging was done with pelvic magnetic resonance imaging and metastatic workup was done with with CECT chest and abdomen. Patients with early stage (T1, 2 or N0) underwent upfront surgery in the form of LAR or APR and patients with locally advanced cancer (T2N+, T3N0/N+, T4N0/N+) were subjected to NACRT before surgery. Patients were treated with a total dose of 50Gy in 25 fractions at a rate of 2Gy per fraction over 5 weeks. After NACRT patients were reassessed after 6 weeks and detailed clinical examination, pelvic MRI, CECT chest and abdomen were done. mrTRG was done as per MERCURY study guidelines with mrTRG score of 1, 2 taken as good response and a score of 3-5 taken as a poor response to NACRT.[10] Based on clinical improvement, patients underwent surgery as LAR/APR. pTRG according to modified Dworak grading system was done with pTRG score of 1, 2 categorized as poor response group and score of 3, 4 categorized as good response group.[15] Analysis of correlation between mrTRG and pTRG was done. All the samples were analysed by two pathologists who followed uniform criteria.

Statistical analysis

All the primary data was initially recorded in the format of MS Excel Worksheets. Microsoft word and excel were used to generate graphs and tables. The correlation of mrTRG with pTRG was analysed by univariate analysis using NCSS version 12.05 statistical software. A $p<0.05$ was considered to be statistically significant.

RESULTS

Out of 79 patients, 10 (12.65%) had clinical stage I, 21 (26.58%) patients had stage II and 48(60.75%) patients had stage III disease. Ten (12.66%) underwent upfront surgery and 69 (87.34%) patients received NACRT followed by surgery. Two patients undergoing upfront surgery were upstaged to pathological stage III. Patients receiving NACRT had pathological stage 0 (6 patients), stage I (30 patients), stage II (21 patients) and stage III (12 patients).

Age distribution

Age of the patients in our study ranged from 16years to 80 years. The mean age was 42 years. Maximum patients i.e., 18, came in the age group of 50-59 years. Distribution of patients in different age groups in tabular form is given as below.

Table 1: Age distribution.

Age groups (years)	N	Percentage (%)
10-19	3	3.80
20-29	15	18.98
30-39	16	20.25
40-49	15	18.98
50-59	18	22.78
60-69	9	11.39
70-79	2	2.53
80 and above	1	1.26

Clinical TNM staging

In study 10 (12.65%) patients had stage I (cT1N0, cT2N0), 21 (26.58%) had stage II (cT3N0, cT4N0) and 48 (60.75%) had III (cT1-4, N+) rectal cancer (Figure 1).

Treatment allocated

Ten (12.66%) patients underwent upfront surgery and 69 (87.34%) patients underwent NACT/RT followed by surgery (Figure 2).

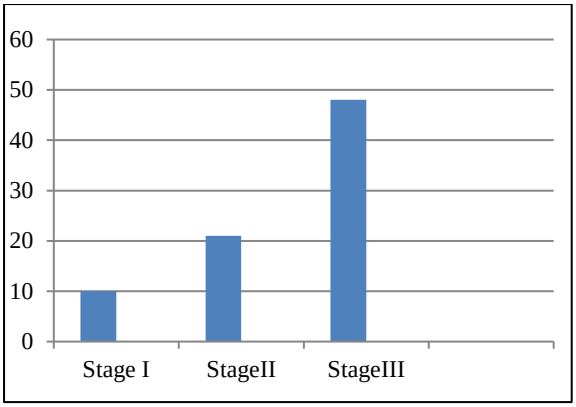

Figure 1: Clinical TNM staging.

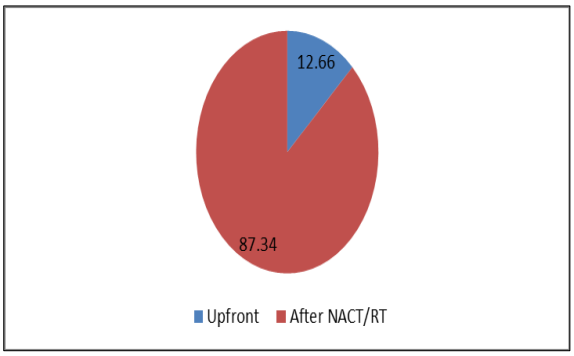

Figure 2: Treatment allocated to study patients.

Operative procedure

The 26 (32.91%) patients had low anterior resection performed on them and 53 (67.09%) patients had abdominoperineal resection as the procedure done.

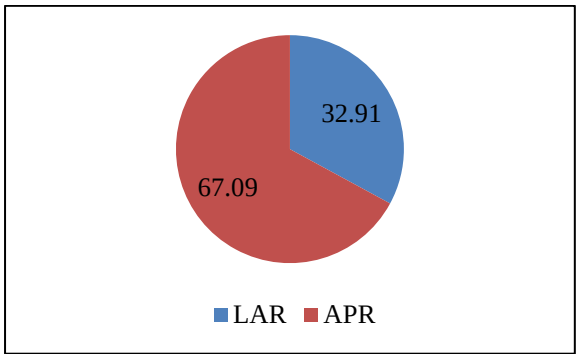

Figure 3: Surgical procedure performed.

Pathological TNM staging

Patients undergoing upfront surgery for early rectal cancer (cT2N0) were having pathological stage I (pT2N0) in 8 patients and stage III (pT2N+) in 2 patients. Out of 69 patients who had preoperative NACT/RT, 6 (8.69%) patients had stage 0 (ypT0N0), 30 (43.47%) patients had stage I (ypT1-2, N0), 21 (30.43%) patients had stage II (ypT3-4, N0) and 12 (17.39%) patients had stage III (ypT3-4N+).

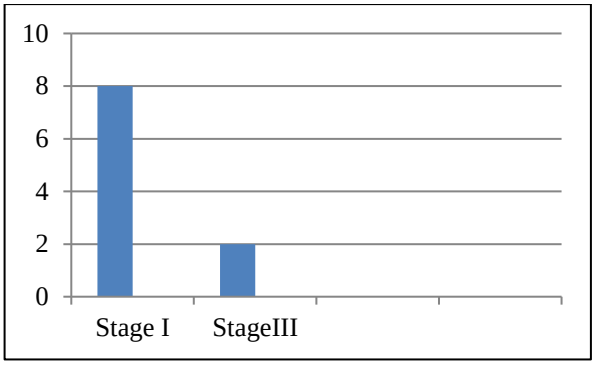

Figure 4: Pathological TNM staging.

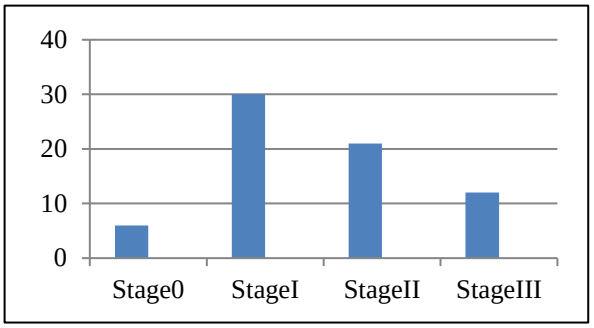

Figure 5: Pathological staging in preoperatively treated patients.

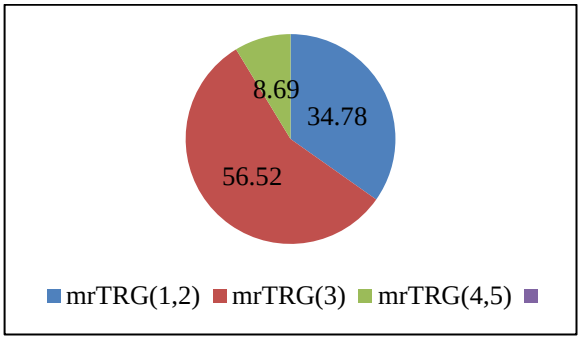

Figure 6: MRI response assessment after NACT/RT.

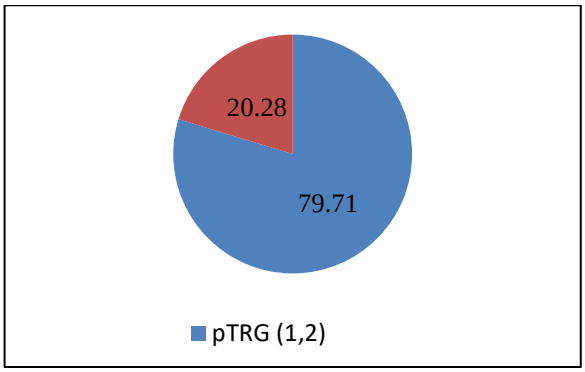

Figure 7: Pathological tumor regression score after NACT/RT.

Pathological staging after upfront surgery in shown in Figure 5.

pTRG

The 14 (20.28%) patients had good pathological response after NACT/RT with a pTRG score of 3, 4 and 55 (79.71%) patients had poor pathological response with a pTRG score of 1, 2.

MRI tumor regression grading

Out of 69 patients who underwent neoadjuvant CT/RT before surgery, 24 (34.78%) patients had good response with mrTRG score of 1, 2; 39 (56.52%) patients had intermediate response with mrTRG score of 3 and 6 (8.69%) patients had poor response with mrTRG score of 4, 5.

Correlation of mrTRG with pTRG is shown in Table 2.

Table 2: Correlation of mrTRG with pTRG.

Clinical variable	Groups	Pathological variable		(X^2)	P value	Statistical sig. p<0.05
		pTRG				
		Good response (3, 4)	Poor response (1, 2)			
mrTRG	Good response (1, 2)	8	16	3.8712	0.049122	Yes
	Poor response (3-5)	6	39			

DISCUSSION

In our study 10 (12.66%) patients diagnosed as early stage rectal cancer and 69 (87.34%) patients were diagnosed as locally advanced rectal carcinoma. Locally advanced cases underwent preoperative chemoradiotherapy. Good response (mrTRG grade 1-2) was seen in 24 (34.78%) patients and poor response (mrTRG grade 3, 4 and 5) was seen in 45 (65.21%) patients. On assessment of histopathological specimen, 08 (11.59%) patients had pathological good response (pTRG grade 3, 4) as predicted by mrTRG, 06 (8.69%) patients had good pathological response (pTRG grade 3, 4) but were predicted as poor responders on mrTRG; 16 (23.18%) patients had poor response predicted on mrTRG and confirmed by pTRG. The sensitivity and specificity of mrTRG 1-2 for prediction of complete pathological response is 57.14% and 70.91% respectively.

Fang et al in a study of 106 patients noted complete response (mrTRG1) in 15 (14.15%) patients and partial response or poor response in 90 (84.90%) patients. Pathological complete response (pTRG4) was seen in 15 (14.15%) patients, good response (pTRG3) in 37 (34.90%) and poor response (pTRG1-2) in 54 (50.94%) patients.[16] Sclafani et al noted that sensitivity and specificity of mrTRG1-2 (complete/good radiological regression) for the prediction of pathological complete response was 74.40% and 62.80% respectively and concluded that agreement between mrTRG and pTRG is low and mrTRG cannot be used as a surrogate of pTRG.[17] Rengo et al noted that sensitivity and specificity of mrTRG for identification of complete pathological responders is 78.26% and 97.62% and concluded that the agreement between pTRG and mrTRG was excellent.[18] Chen et al in a study of 52 patients of mid to lower rectal cancer noted an accuracy of magnetic resonance imaging of 52% in T staging and 68% in N staging for agreement. Poor agreement between post CT/RT MRI and pathological staging was observed. The problem with MRI was believed to be that it could not completely differentiate fibrosis from viable residual tumors.[19] Limitation of our study is that being a prospective observational study and not a randomized control trial, it does not represent level 1 evidence. It was purely a descriptive (prospective observational) single centre study about patients undergoing TME irrespective of the modality of treatment received. So, differences between upfront surgery and post NACT/RT groups was not taken into consideration.

CONCLUSION

There was a rising trend for younger age of presentation in our study. Male to female ratio was approximately 2:1. Majority of patients presented with carcinoma lower rectum for which APR was done and 60% of patients presented with locally advanced (Stage III) rectal cancer. There is a statistically significant agreement between mrTRG and pTRG. mrTRG grading can be used as a reliable predictor of pathological response. Our study concluded that mrTRG is good predictor of pathological response and thus a prognosticator of completeness of resection. So, efforts should be made to do a mrTRG scoring in each patient as it not only provides oncological safety but also reduces post operative mortality.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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