Section: Research Paper

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

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Abstract

Background and Aim: Colorectal cancer is fourth most common cancer worldwide . In India, Annual incidence rates for colon cancer and rectal cancer in men are 4.4 and 4.1per 100000 respectively. 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).

Materials and Method: A total of 158 patients who satisfied the inclusion and exclusion criteria were included in the study. 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.

Results: The good pathological response was found in 28 patients. They had undergone NACT with a pTRG score of 3 and 4. Poor pathological response was seen in 110 patients with score of 1 and 2. Out of 138 patients who had underwent the process of neoadjuvant CT/RT before surgery, the good response with mrTRG score 1 and 2 was found in 48 patients and intermediate response was seen in 78 patients with mrTRG score of 3 and poor response with mrTRG score of 4 and 5 was found in 12 patients.

Conclusion: Colorectal cancer is a disease originating from the epithelial cells lining the colon or rectum most frequently as a result of mutations in the Wnt signaling pathway that increase signaling activity. Present 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.

Keywords: rectal cancer, upront surgery, neoadjuvant chemoradiotherapy, mrTRG, pTRG

Introduction

Colorectal cancer is fourth most common cancer worldwide. In India, Annual incidence rates for colon cancer and rectal cancer in men are 4.4 and 4.1per 100000 respectively.[1] The Annual incidence rate for colon cancer in women is 3.9 per 100000.Colon cancer ranks 8th and rectal cancer ranks 9th among men. For women, rectal cancer does not figure in the top10 cancers, whereas colon cancer ranks 9th.[1, 2]

Several risk factors have been implicated in rectal tumorigenesis including genetics, age, obesity, smoking, and diet. Cancers of the rectum and rectosigmoid junction account for 30% of all CRC diagnosed. Rectal cancer is defined as tumours arising within 15 cm of the anal verge.[3]

Currently, the standard treatment for stage II/III rectal cancer is preoperative chemoradiotherapy (PCRT) followed by surgery and adjuvant chemotherapy.[4] PCRT is effective in reducing local recurrence and down staging locally advanced rectal cancer. However, it is associated with complications such as bowel, anorectal, and sexual dysfunctions and delay from surgical recovery.[5]

The addition of PCRT also led to a decrease in tumor size and local relapse rate and an increase in disease-free survival (DFS); however, it did not have an impact on overall survival (OS). Thus, the need to control distant metastasis poses as a challenging issue[6]. Although radiotherapy is an effective means of local control, complications such as anastomotic leakage, sexual dysfunction, and fecal incontinence are very common in patients receiving radiotherapy in the pelvic area[7]

The current standard therapy for patients with locally advanced rectal cancer (LARC) is neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision (TME) and postoperative adjuvant chemotherapy. This trimodal therapy provides excellent local tumor control and long-term survival. Although some patients achieve a complete response to neoadjuvant CRT, several do not experience tumor regression.[7]

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 predicts 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.[8] 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.[8, 9]

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.[10] 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.[11]

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.[12] This study was conducted in the medical college, on all preoperatively NACRT treated colorectal resected specimens received for routine histopathological evaluation from Departments of Surgery and Surgical Oncology.

Materials and Method

The present analysis is the observational prospective analysis. The preoperative details were recorded from the patients history. The study was done in the department of the surgery, medical college and associated hospital. The ethical committee was informed about the study and the ethical clearance certificate was obtained prior to the start of the study.

The inclusion criteria followed in the study was consecutive patients of operable mild and lower rectal cancers that underwent NACRT in the period of two years. The patients who had distant metastasis or had presentation of obstruction and perforation were excluded from the study. 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.

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.

All the preoperatively NACRT treated colorectal resected specimens were received in the Pathology Department in 10% formalin. In every case the standard protocol for surgical grossing of resected specimens was followed. As per standard protocol after conventional processing in a Leica 120 model histokinette and embedding in paraffin wax, paraffin embedded tissue blocks were made. For microscopic examination, 5 µm thick paraffin sections was cut and stained with haematoxylin and eosin (H &E). In those cases with apparent complete pathological response after receiving complete NACRT, In addition, 4µm sections were cut from a paraffin block of tumour tissue and taken on a glass slide coated with adhesive poly-L-lysine for immunohistochemistry (IHC) Cytokeratin was done to confirm the absence of tumour cells.

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

A total of 158 patients who satisfied the inclusion and exclusion criteria were included in the study. Of the total included patients, the clinical stage I was found in 20 patients, stage II was found in 42 patients and 6 patients had clinical stage III disease. There were 20 patients who underwent upfront surgery. In 138 patients; they received NACRT that was followed by surgery. Four patients undergoing upfront surgery were upstaged to pathological stage III. Patients receiving NACRT had pathological stage 0 (12 patients), stage I (60 patients), stage II (42 patients) and stage III (24 patients).

Age of the patients in our study analysis ranged from 18 years to 70 years. The mean age was 40 years. Maximum patients i.e., 36 came in the age group of 50-59 years. The TNM staging of the study showed 20 patients had stage I (cT1N0, cT2N0), 42 had stage II (cT3N0, cT4N0) and 96 had III (cT1-4, N+) rectal cancer. In the treatment protocol there were 20 patients who underwent upfront surgery. In 138 patients; they received NACRT that was followed by surgery.

The 52 patients had low anterior resection performed on them and 106 patients had abdominoperineal resection as the procedure done.

Patients undergoing upfront surgery for early rectal cancer (cT2N0) were having pathological stage I (pT2N0) in 16 patients and stage III (pT2N+) in 4 patients. Out of 138 patients who had preoperative NACT/RT, 12 patients had stage 0 (ypT0N0), 60 patients had stage I (ypT1-2, N0), 42 patients had stage II (ypT3-4, N0) and 24 patients had stage III (ypT3-4N+).

The good pathological response was found in 28 patients. They had undergone NACT with a pTRG score of 3 and 4. Poor pathological response was seen in 110 patients with score of 1 and 2. Out of 138 patients who had underwent the process of neoadjuvant CT/RT before surgery, the good response with mrTRG score 1 and 2 was found in 48 patients and intermediate response was seen in 78 patients with mrTRG score of 3 and poor response with mrTRG score of 4 and 5 was found in 12 patients.

Table 1: Correlation of mrTRG with pTRG

Clinical Variables	Groups	Pathological variable		Statistical analysis
		pTRG		
		Good response 3,4)	Poor response (1,2)	
mrTRG	Good response (1,2)	16	32	Yes
	Poor response (3-5)	12	78	

Discussion

Colorectal cancer is a disease originating from the epithelial cells lining the colon or rectum most frequently as a result of mutations in the Wnt signaling pathway that increase signaling activity. most probably occur in the intestinal crypt stem cell.[13] Human CRCs can be broadly classified into two major categories based on their molecular profiles: nonhypermutated microsatellite stable (MSS) CRCs• hypermutated microsatellite instability (MSI) cancers.[14]

The most commonly mutated gene in all colorectal cancer is the APC gene, which produces the APC protein. These genes are normally important for stem cell renewal and differentiation, but when inappropriately expressed at high levels, they can cause cancer.[15] Comprehensive, genome-scale analysis has revealed that colorectal carcinomas can be categorized into hypermutated and non-hypermutated tumor types. The common theme among these genes, across both tumor types, is their involvement in WNT and TGF-β signaling pathways, which results in increased activity of MYC, a central player in colorectal cancer.[16]

In the present study 20 patients were diagnosed with early stage rectal cancer and in 138 patients were diagnosed with advanced rectal carcinoma. The patients diagnosed with advanced carcinoma underwent the process of chemo radiotherapy. Good response (mrTRG grade 1-2) was seen in 48 patients and poor response (mrTRG grade 3, 4 and 5) was seen in 90 patients. On assessment of histopathological specimen, 16 patients had pathological good response (pTRG grade 3, 4) as predicted by mrTRG, 12 patients had good pathological response (pTRG grade 3, 4) but were predicted as poor responders on mrTRG; 32 patients had poor response predicted on mrTRG and confirmed by pTRG.

Fang et al[17] 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. Rengo et al[18] 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.

Conclusion

Present 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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