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Original Research Article

Neoadjuvant chemoradiation for down staging of locally-advanced rectal cancer, and assessment of clinical response with digital rectal examination, magnetic resonance imaging and colonoscopy

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ABSTRACT

Background: In this era of total neoadjuvant treatment (TNT) followed by rectal preservation non-operative management (NOM) or wait and watch (WW) approach for non-metastatic locally-advanced rectal cancer (LARC), reliable and reproducible response evaluation to neoadjuvant therapies forms the cornerstone. Through this study, we try to evaluate clinical response of locally-advanced rectal cancer to neoadjuvant chemoradiation (CRT) in terms of downstaging and total mesorectal excision (TME), and the accuracy of digital rectal examination (DRE), magnetic resonance imaging (MRI) and colonoscopy in the assessment of clinical response to neoadjuvant CRT.
Methods: Histologically proven locally advanced rectal adenocarcinoma patients, after pretreatment evaluation, were considered for neoadjuvant chemoradiation, i.e., intensity-modulated radiation therapy (IMRT) with 5-fluorouracil (5-FU) and leucovorin-based concurrent chemotherapy. Patients were evaluated 6-8 weeks after completion of CRT and clinical response assessed by means of DRE, colonoscopy and MRI of pelvis. Following surgery, pathological response was assessed on the final histopathological examination (HPE).
Results: Twenty-two patients were accrued for this protocol, of which, 15 (68.2%) were male and 7 (31.8%) were female. Downstaging and TME was achieved in 90.9% of the patients. The sensitivity of DRE, colonoscopy and MRI to detect a complete response was 66.67% and specificity was 94.74%. There were no severe toxicities or deaths reported.
Conclusions: Neoadjuvant concurrent chemoradiotherapy with bolus 5-FU and leucovorin is an accepted modality of treatment for locoregionally-advanced rectal cancer, which offers higher rates of downstaging and TME. Digital rectal examination, colonoscopy and MRI together can be reliably used to assess response following neoadjuvant CRT.

Keywords: Locally-advanced rectal cancer, Neoadjuvant chemoradiation, Downstaging, Response assessment, Accuracy

INTRODUCTION

Colorectal cancer (CRC) is a formidable health problem worldwide. According to the World Health Organization (WHO) 2022 Globocan data, rectal cancer is the eighth leading cancer worldwide with an incidence of 729,833 (7.1%) new cases. In India, colorectal cancer is the sixth leading cancer (70,038; 5.0%), while being the fourth leading site-specific cancer in males (43,360; 6.3%) and fifth in females (26,678; 3.7%).[1]

Radical surgery still remains the principal curative treatment. However, upfront surgery alone in locally-advanced rectal cancer (LARC) was found to be associated

with high rates of local pelvic relapses.[2] Local recurrences have been reduced from 40% to <10% with the help of multidisciplinary treatments.[3] Total mesorectal excision (TME), which involves anatomical resection of rectum along with the enveloping mesorectal fascia along embryological planes, has been able to mitigate the problem of local pelvic recurrences and is now the standard surgical approach.[4,5] Furthermore, the introduction of neoadjuvant chemoradiation (CRT) has helped achieve exceedingly improved local control and higher rates of sphincter-preservation surgeries in low lying tumors, with acceptable rates of toxicities.[6-8]

This study was undertaken to establish the accuracy of digital rectal examination (DRE), pelvic magnetic resonance imaging (MRI) and colonoscopy in assessing clinical response after neoadjuvant CRT in LARC, in terms of downstaging and rates of total mesorectal excision.

METHODS

This is a prospective observational study undertaken in Karnataka Medical College and Research Institute (KMCRI) Hubballi from December 2019 to December 2021. The study included a total of 22 patients aged between 18-65 years, with histologically proven newly diagnosed locally-advanced (T3 and T4) adenocarcinoma of mid- and lower-third rectum, with node positive disease, with Karnofsky performance score (KPS) of 70 or more. Patients with stage I disease or distant metastases, uncontrolled comorbid conditions, prior oncological interventions and histological variants other than adenocarcinoma were excluded from the study.

The aforementioned eligible patients were considered for neoadjuvant CRT after obtaining informed written consent. Pre-treatment evaluation of patients were done by complete medical history, physical examination, complete blood count, serum biochemical test, serum carcinoembryonic antigen (CEA) levels, chest X-ray, colonoscopy, biopsy and MRI of abdomen and pelvis with T2 and diffusion weighted imaging sequences, and the disease was staged as per UICC staging of tumors. Immobilization of patients was done using thermoplastic mould in supine position. Computed tomography (CT) simulation was obtained by taking 2 mm cuts after giving iodine contrast. Radiotherapy was planned using Intensity-modulated radiation therapy (IMRT) technique from a LINAC (CLINAC 2100), and was given for 6 weeks with a dose of 45-50 Gy in 25-28 fractions with concurrent chemotherapy of 5-flurouracil (5-FU) 400 mg/m^2 IV bolus with leucovorin 20 mg/m^2 for 4 days during weeks 1 and 5 of CRT. Weekly assessment for skin and gastrointestinal (GI) and haematological toxicities. Patients were evaluated 8 weeks after completion of CRT with DRE, pelvic MRI and colonoscopy to assess the clinical response.

Digital rectal examination findings were classified as: normal bowel wall- complete response, subtle residual abnormality of the bowel wall- partial response, and obvious residual tumor- no response.

MRI findings were classified as: normalized rectal wall or only subtle wall hypointense wall thickening and no involved nodes- complete response, small residual isointense mass and/or involved nodes- partial response, pronounced hypointense wall thickening without isointense signal and no involved nodes- partial response, and gross residual isointense mass and/or involved nodes- no response.

Colonoscopic findings were classified as: Absence of ulcers and mucosal irregularity, flat white scar, telengiectasia- complete response, Small mucosal nodules or irregularities, superficial ulceration, mild erythema of scar- partial response, and visible tumor- no response.

Surgery was performed 8-10 weeks after chemoradiation. the tumor along with the mesorectal lymph nodes were sent for histopathological examination (HPE), and pathological response was assessed, which was graded as complete response, partial response and no response.

Statistical analysis was carried out with statistical package for the social sciences (SPSS) version 26.0 (IBM, NY, USA) and Microsoft word and excel have been used to generate graphs and tables. Results on continuous measurements are presented in mean±SD (min-max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance (p value ≤0.01). Paired nominal data are analyzed by McNemar test. Stuart Maxwells (marginal homogeneity) test is applied to test for pre and post test variability. Log Rank (Mantel-Cox) test has been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

The age of the patients ranged from 16 years to 62 years, with a median of 46.18 years. Among a total of 22 patients, 15 (68.2%) were male and 7 (31.8%) were female, with a male: female ratio of 2.1:1. The most frequent grades of tumor were grades 2 and 3 (10; 45.5% each) followed by grade 1 (2; 9.10%). Mean length of tumour as measured by colonoscopy was 6 cm. The most common stage at presentation was T4 (11; 50%), followed by T3 (6; 27.35%) and T2 (5; 22.7%) (Table 1). All of the 22 patients had node positive disease.

Treatment outcomes

On evaluation with digital rectal examination, pelvic MRI and colonoscopy, 3 patients (13.6%) had clinical complete response, 16 patients (72.73%) had partial response and 3 patients (13.6%) had no response or stable disease. All of the twenty-two patients underwent abdominoperineal

resection (APR). Twenty patients (90.9%) had circumferential resection margin (CRM) free of disease, and CRM was involved in two patients (9.09%). On histopathological examination, 3 patients (13.6%) had pathological complete response, 16 patients (72.73%) had partial response and 3 patients (13.6%) had no response or stable disease. The median number of nodes harvested was 8.

Toxicity outcomes

Toxicities like haematological and GI toxicities were seen, such as: grade 1 anaemia in 72.7% patients, grade 1 leucopenia in 40.9%, grade 2 neutropenia in 4.5%, and grade 1 GI toxicity in 27.27% patients.

Comparison of clinical evaluation and HPE

Of the 3 patients (13.64%) who had clinical complete response, only 2 (9.09%) showed pathological complete response, whereas, 1 (4.55%) showed a pathological partial response. Sixteen (72.73%) patients showed clinical partial response, among which 15 (68.18%) patients showed pathological partial response, and 1 (4.55%) showed a complete pathological response. Three (13.64%) patients showed no response or stable disease, clinically as well as pathologically (Table 2).

Table 1: Baseline characteristics.

Variables	Count	Percentage
Gender		
Male	15	68.20
Female	7	31.80
T stage		
T2	5	22.7
T3	6	27.35
T4	11	50
Adenocarcinoma grade		
Grade 1	2	9.10
Grade 2	10	45.50
Grade 3	10	45.50
Sphincter		
Not involved	11	50.00
Involved	11	50.00
CRM		
Free	20	90.90
Involved	2	9.10
Clinical response		
Partial/no response	19	86.40
Complete	3	13.60
Pathological response		
Partial/no response	19	86.40
Complete	3	13.60

CRM: Circumferential resection margin

Therefore, clinical evaluation could identify 2 (66.6%) patients accurately with complete pathological response and 18 (94.7%) patients with partial response, hence concluding, that clinical evaluation demonstrated a sensitivity of 66.67% and specificity of 94.74%, with area under curve (AUC) of 0.81 for identifying complete response (Tables 3 and 4).

Table 2: Comparison of clinical evaluation and HPE.

Clinical evaluation	Pathological (%)			
	Com-plete	Partial	No respo-nse	Total
Complete	2 (9.09)	1 (4.55)	0 (0.00)	3 (13.64)
Partial response	1 (4.55)	15 (68.18)	0 (0.00)	16 (72.73)
No response	0 (0.00)	0 (0.00)	3 (13.64)	3 (13.64)
Total	3 (13.64)	16 (72.73)	3 (13.64)	22 (100)

Table 3: Comparison of clinical evaluation and HPE for assessing response.

Clinical evaluation	HPR (%)			Mc Nemar test
	Com-plete	Partial/ no response	Total	
Complete	2	1	3 (13.64)	P=1.00
Partial/no response	1	18	19 (86.36)	
Total	3 (9.09)	19 (90.91)	22 (100)	

Table 4: Validity of clinical evaluation for assessing complete response after chemoradiation.

Parameters	Values	95% CI
Sensitivity (%)	66.67	9.43 to 99.16
Specificity (%)	94.74	73.97 to 99.87
Positive predictive value (%)	66.67	9.43 to 99.16
Negative predictive value (%)	94.74	73.97 to 99.87
AUC	0.81	0.58 to 0.94

Changes in tumor staging pre- and post-chemoradiotherapy

Of a total of 11 patients with T4N1M0 tumors pre-CRT, 4 patients were downstaged to T3N0M0, 3 patients to T2N0M0, 2 patients showed no response or had stable disease, whereas, 2 patients had a clinical complete response. Of the 6 patients with T3N1M0 tumours, 5 patients were downstaged to T2N1M0 and 1 patient had a clinical complete response. Of the 5 patients with T2N1M0 tumours, all 5 of them were downstaged to T2N0M0 (Table 5). Therefore, downstaging was noted in

90.9 % of the cases, although not found to be statistically significant (p=0.004).

Table 5: Changes in tumor staging pre- and post-chemoradiation.

Pre T	Post T				Stuart Maxwell test (marginal homogeneity)
	2	3	4	Total	
2	5	0	0	5	P=0.0047
3	5	0	0	5	
4	3	4	2	9	
Total	13	4	2	19	

Comparison of pre- and post-chemoradiation CEA levels

The mean serum CEA level pre-CRT was 30.86 (range 1.48-106.4), and post-CRT mean serum CEA level was 8.48 (range 0.9-51.31) (Table 6). The difference in serum CEA value between pre- and post-CRT was found to be statistically significant (p<0.001).

Table 6: Comparison of pre- and post-chemoradiation CEA levels.

Parameters	N	Mean (SD)	Median (IQR)	Min	Max	Wilcoxan signed rank test
Pre-CRT CEA	22	30.86 (33.83)	16.55 (3.2-55.2)	1.48	106.4	p<0.001
Post-CRT CEA	22	8.48 (15.57)	2.4 (1.04-4.01)	0.9	51.31	

DISCUSSION

Despite radical surgery being the principal curative treatment in rectal cancer, upfront surgery alone in locally-advanced rectal cancer (LARC) is associated with high rates of local pelvic relapses.[2] Hence, multimodal treatments have been employed to improve outcomes. Neoadjuvant chemoradiation or short-course radiotherapy followed by total mesorectal excision (TME) is currently widely accepted standard of care for LARC. Significantly fewer local recurrences have been noted with TME, by means of complete resection of locoregional lymphatic tissue enveloping the mesorectal fascia. The argument for neoadjuvant CRT in resectable disease is based primarily on possible downstaging of tumors close to the circumferential resection margin or the sphincter apparatus, thereby enhancing both R0 resections and sphincter preservation rates. Neoadjuvant CRT has been shown to induce upto 15-25% cCR, while 20-25% of cCR after surgery showed pCR.[9-11] Studies have shown that complete response or TNM downstaging after neoadjuvant CRT are associated with favorable oncological outcomes in LARC.[12-14] Possible concerns of preoperative CRT include an increase of both local and systemic toxicity and over treatment of inaccurately staged patients. Several studies using preoperative CRT have shown a promising tumor response with acceptable toxicity.[15,16]

In recent years, there has been a paradigm shift towards rectal preservation non-operative management (NOM) and total neoadjuvant therapy (TNT), which includes CRT followed by consolidation chemotherapy (CCT). Thereby avoiding radical proctectomy, coloanal anastomosis and permanent colostomy, and the resultant sequelae of major pelvic surgery.[17,18] This demands a reliable method to assess response to neoadjuvant therapy.

In the studies by Habr-Gama et al who explored nonoperative treatment for CR in a wider group of patients, DRE and endoscopy served as main selection tools.[10,11] Digital rectal examination (DRE) may detect subtle mucosal irregularities, although, subjective and only possible for low-lying rectal cancers. Studies showed that DRE correctly identifies cCR in only upto 21% patients with confirmed pCR.[19,20] About 90% of local recurrence is known to occur within the lumen and is detectable endoscopically.[21] Studies have shown a 78.5% sensitivity and 86.9% specificity, with AUC of 0.70 for endoscopy alone in assessment of clinical response.[22] An Ogura et al study demonstrated an accuracy of 91.7%, sensitivity of 27.8% and specificity of 100% with endoscopy for assessment of clinical response.[23] Endoscopy only provides information regarding intraluminal findings. However, the evaluation of mesorectum for nodal disease requires a multimodal approach, thereby necessitating imaging modalities. MRI can provide this additional information, which can be critical for decision making. However, Schnall et al demonstrated a sensitivity of only 81% for T stage and 72% for N stage with MRI alone.[24] In another study by Tatli et al, MRI demonstrated a sensitivity of 93% and specificity of 86% for T stage.[25]

It was therefore concluded that multimodal assessment adds to the accuracy of detecting response. The 2022 Chen et al study demonstrated a sensitivity of 71.43%, specificity of 56.52% and AUC of 0.693 by a combination of DRE and endoscopy. Whereas, a combination of MRI and endoscopy showed a sensitivity of 21.43%, specificity of 97.78% and AUC of 0.687.[22] A combination of MRI and endoscopy demonstrated a sensitivity of 52.9% and specificity of 96.5%, with an AUC of 0.882, in a study by Ko et al.[26] In a study by Maas et al, the sensitivity of DRE, colonoscopy and MRI combined was found to be 71% and specificity of 97%, with AUC of 0.89.[27] Our study however, demonstrated a sensitivity of detecting a complete response with a combination of DRE, colonoscopy and MRI of 66.67% and specificity of 94.74%, with an AUC of 0.81.

A 1999, M.D. Anderson Cancer Centre study revealed a 62% downstaging following neoadjuvant CRT.[28] Another study by Kim et al demonstrated an overall downstaging

rate of 84% in both primary tumor and nodes following preoperative CRT.[29] Our study however, achieved downstaging and TME in 90.9% of patients, 13.6% of the patients had clinical complete response and 9.09% of the patients had pathological complete response.

Limitations

Locally advanced rectal cancer patients including T2-T4 and node positive disease have been included in the study, with varying degree of response in different stages, making it a heterogenous study population. Pathological types of adenocarcinoma have not been individually analyzed for response. Another limitation of the study includes the interobserver variation in documentation of colonoscopy and MRI findings, thus making it subjective.

CONCLUSION

The results of this study confirm that neoadjuvant chemoradiotherapy with 45-50 Gy in 25-28 fractions with bolus 5-FU and leucovorin achieves comparable results in terms of downstaging and TME. Also, digital rectal examination, MRI and endoscopic evaluation can be used reliably in post-neoadjuvant chemoradiation restaging.

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