

The Outcome of Neoadjuvant Chemo Radiotherapy and Surgery in Carcinoma Rectum: Our Experience

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Abstract

Introduction: Carcinoma of the rectum is not only a medical but a social problem. Adenocarcinoma of the rectum accounts for 30% of these cancers. Locally advanced cancers of the rectum i.e., stage 2 and 3 diseases prove to be a challenge with respect to its management. Present guidelines state that the use of neoadjuvant chemoradiotherapy to downstage the locally advanced carcinomas of the rectum to have a positive impact on not only the survival but also the quality of life post-treatment viz., by allowing better resection margins to preserve the sphincter mechanism by performing a coloanal anastomosis.

Objectives: To assess the locoregional response rates determined by the measurement of margin of clearance from the anal verge, organ preservation (sphincter-saving operations), and histopathological findings in post CRT surgical specimen.

Materials and methods: This study included a total of 33 patients which were diagnosed with locally advanced rectal cancer who presented in the department of General Surgery, Vydehi Hospital, Bangalore. The patients in this series were subjected to pre-operative CRT, loco-regional response rates and the number of sphincter preserving surgeries performed were assessed.

Results: Downstaging of the tumor was achieved in 91% of the cases.

Conclusion: From this study, an interpretation can be made that following CRT there is a significant downstaging and increased ability to perform sphincter-saving procedures.

Keywords: Chemoradiotherapy; Rectum; Carcinoma; Mortality; Morbidity

Introduction

Rectal cancer is a form of cancer that is being increasingly observed in Indian population with increase in the migrant population to the west due to change in diet and lifestyle habits [1] accounting for over a third of mortality and morbidity worldwide in cancer cases [2]. The lack of a peritoneal covering for the most part of the rectum is a major reason for the higher risk for local recurrence after primary surgical management.

Recent studies have shown that preoperative chemo radiotherapy has better remission rates compared to stand-alone surgery. It especially has increased benefit and has become the standard of treatment for locally advanced cases of carcinoma rectum viz., [stage 2 {cT3-4N0M0} and stage 3 {cT1-4N1-2M0}] with the advantage of better local control, low toxicity rates and reducing local recurrence [3]. In order to increase the number of sphincter preserving operations performed, studies cite the use of preoperative chemo radiation as a means to decrease the local recurrence rate [4]. Sphincters saving operations with a distance of the tumor more than 6-7 cm from the anal verge have been found to have better 3-year survival rates [5]. However, the effectiveness of such treatment in the Indian context and conditions is still uncharted territory.

Aim

To evaluate the impact of neoadjuvant chemoradiotherapy on:

- Loco-regional response rates determined by the measurement of the margin of clearance from the anal verge.
- Organ conservation (sphincter saving operations).
- Histopathological findings post CRT surgical specimen.

Materials and Methods

Data collection

The period of study was from November 2014 to June 2016 in the department of General Surgery in Vydehi hospital. Data collected was recorded in a specifically designed case record proforma pertaining to patient particulars, history details, clinical examinations, investigations, diagnosis, surgical procedures and follow-up.

Study design

Observational study-case control study.

Inclusion criteria

- Patients presenting with carcinoma rectum confirmed by clinical examination and relevant investigations.
- Locally advanced rectal carcinomas i.e., stage 2{cT3-4N0M0} and stage 3{cT1-4N1-2M0}.

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Received December 12, 2017; **Accepted** December 22, 2017; **Published** December 29, 2017

Citation: Vinay HG, Vybhav R. The Outcome of Neoadjuvant Chemo Radiotherapy and Surgery in Carcinoma Rectum: Our Experience. 2017; 13(4): 123-126 DOI: [10.7438/1584-9341-13-4-3](https://doi.org/10.7438/1584-9341-13-4-3)

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Exclusion criteria

- Patients aged <18 yrs.
- Stage 1 and 4 rectal carcinoma.

Methods

A Detailed History and Physical Examination of all patients admitted were evaluated by documenting the history and a thorough clinical examination. In history, importance was given to presenting complaints, duration of symptoms, previous surgical treatment or any other co-morbidity. Physical examination was carried out in all patients as per the case record proforma. Following this, the patients were subjected to routine workup and certain relevant specific investigations such as USG, colonoscopy and guided biopsy, CECT of abdomen and pelvis and serum levels of carcino embryonic antigen.

The patients then underwent treatment after a diagnosis of locally advanced carcinoma of rectum was made. Then a decision whether to put the patient through neoadjuvant chemoradiotherapy was taken. After neoadjuvant therapy, the down-staging was appreciated based on the ability to perform a sphincter-preserving surgery. The resected specimen was sent for histopathological examination (HPE) and staging was done. Appropriate antibiotics and analgesics were administered postoperatively for all cases. If required adjuvant chemotherapy was given postoperatively also.

Statistical analysis

The statistical analysis was performed by STATA 11.2 (College Station TX USA). Shapiro Wilk test has been used to find the normality, Students paired t-test were used find the pre and post CRT comparison of distance from anal verge and CEA, Chi-square test was used to measure the association between the Pre and post comparison of TNM Stage and those expressed as frequency and percentage. The age distribution, gender distribution, symptoms, downstaging of post CRT, historical grade of differentiation, type of surgery, histopathology free margins, colonoscopy findings, complications, ultrasound post CRT and DRE were expressed as frequency and percentage. $P < 0.05$ is considered as statistically significant (Figures 1 and 2).

Results

Of a total of 33 patients in the study, the maximum number of cases with locally advanced malignancy was found in the age group between 31-40 years and 51-60 years with a percentage of 24%. Mean age was 45.36, SD 15.82 and range 3-80. So it is common in the middle and old age. In this group, males were found to be a majority with 19 of 33 accounting for 58%, the female population in the study was 42% from which it was inferred to be more common among males.

With regards to the clinical features, the most common presentation was growth in the rectum found in DRE seen in all patients. 97% presented with bleeding per-rectum and 16 of them (50%) had a history of altered bowel habits i.e., diarrhea which was more common in the morning. 18 had a history of loss of weight and appetite was another significant symptom seen in patients with a percentage of 55%. 21 patients (65%) were found to have pallor.

When comparing TNM stages pre and post CRT it can be seen that there were 4 patients of T1 group pre-CRT and post-CRT all remained with T1 staging. There were 9 patients with T2 lesion pre-CRT, post-CRT 5 patients remained in T2 stage and in 4 patients regression was seen to T1. Of a total of 10 patients with T3 stage, after CRT 1 patient was retained in the same stage, 3 regressed to T2 and in 6 patients regression was seen to T1. Pre-CRT 10 patients with T4 lesion which after CRT 2 remained as T4, 3 reduced to T3 and 5 to T2. No patient

became T1 after CRT in T4 lesions. From this we could get a p-value of 0.02 which was found to be significant and thus proved the fact that there is a significant reduction in the TNM staging following CRT (Table I).

From, the table above an inference can be made that there is significant down-staging that occurred in the TNM staging in 91% of the patients accounting for 30 out of the 33 patients and 3 patients did not show any change in the TNM stage following Neoadjuvant CRT which accounted for 9% of the cases. It was thus inferred that there is down-staging which occurred following CRT and was found to be significant (Figure 3).

The distance of the tumour from the anal verge was analysed and the average pre-CRT distance was 2.79 cm with a standard deviation of 1.08 cm when the same was analysed post-CRT an average distance of 7.74 (± 1.55 cm) was seen from anal verge which achieved a significant p-value of 0.01. This reassured the fact of tumour regression and better resectability rates and also the ability to be able to perform a sphincter-preserving surgery which requires a distance of 6-10 cm from the anal verge. This study result obtained in this table is well within this prescribed limit.

The histopathology of the tumour was evaluated and was found that 76% (25/33) were of moderate grade which was the most common



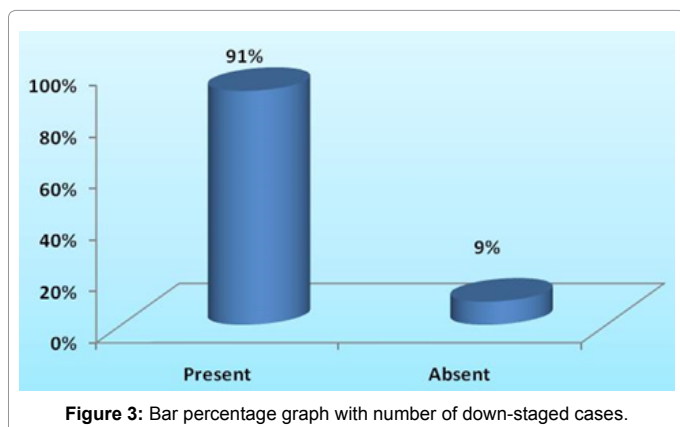
Figure 1: Showing line graph of number of cases in each stage pre-CRT.



Figure 2: Line graph of the number of cases down-staged in each stage post-CRT.

Table I: Showing line graph of number of cases in each stage pre-CRT.

Pre	TNM Stage Post CRT				Total	P-Value
	T1	T2	T3	T4		
T1	4	0	0	0	4 (12%)	0.02
T2	4	5	0	0	9 (28%)	
T3	6	3	1	0	10 (30%)	
T4	0	5	3	2	10 (30%)	
Total	14 (42%)	13 (39%)	4 (12%)	2 (6%)	33	



and 5 patients i.e., 15% had a well-differentiated grade and 3 (9%) were of poorly differentiated variety. Post CRT patients were compared with respect to the type of surgical procedure which was possible to be performed. As per this post CRT following down-staging 58% of the patients (19/33) we see that a sphincter-preserving LAR was possible to be performed and 8/33 patients (24%) underwent AR. One patient was seen to undergo APR and APR with colostomy each and 1/33 palliative colostomy accounting for a percentage of 3 each. In this series, there were 2 deaths accounting for 3% each. In this one died post CRT due to toxicity and one died due to causes unrelated to the study.

As far as the histopathological specimen analysis is considered 85% of the patients were found out to be adenocarcinoma of the rectum with negative margins for tumor and 1 patient was found to have positive margins for tumor with a histopathological specimen being adenocarcinoma. In a single patient due to poor clinical status only palliative colostomy was done and 3 patients (9%) were lost to treatment or died before surgery.

The complications were evaluated statistically in all cases. In 28 patients (85%) there were no complications, 1 patient had anastomotic leak which was minor and was managed conservatively. Three patients developed surgical site infection and one patient had faecal incontinence post operatively.

In the 3 months follow-up patients were also evaluated with respect to any new growth found on DRE and it is seen that in 87% of the patients did not have any growth. 6 percent of the patients which included 2 patients died in follow-up period. In 1 patient no change was seen in the preoperative period and mass was felt per rectum on examination. In 3 patients no follow-up was possible as they were not compliant with the follow-up requirements.

Discussion

Laisharam R et al. [6] have reported a maximum number of cases between 60-69 years. In a study conducted by Ibrahim et al. [7] maximum number of cases seen with age less than 40 yrs. But in present study series, most patients were between 30-60 years. The prevalence of tumors in present study series was slightly higher in males and was in the ratio M:F-1.38:1. Laisharam R et al. [6], Ibrahim et al. [7], and Shyamal et al. [8] studies reported tumors more commonly in males. In Aldridge MC et al. study tumors were more common in females.

On comparing the clinical features in studies conducted by Shyamal et al. [8] and Hamilton et al. [9] it is seen that rectal bleed was the most common symptom which was in accordance with our study. There was the incidence of loss of weight and appetite in 55% of the patient in the present study. In a study conducted by Hamilton W et al. [9], it was found out that 94 cases of 349 and 92 controls of 1744 patients had loss of weight. Altered bowel habits were seen in 223 cases of 349

and 429 controls of 1744 patients. In the present study, 16/33 patients accounting for 50% of the cases had similar symptoms. Anemia in the present study was seen 65% patients and had clinical pallor [9].

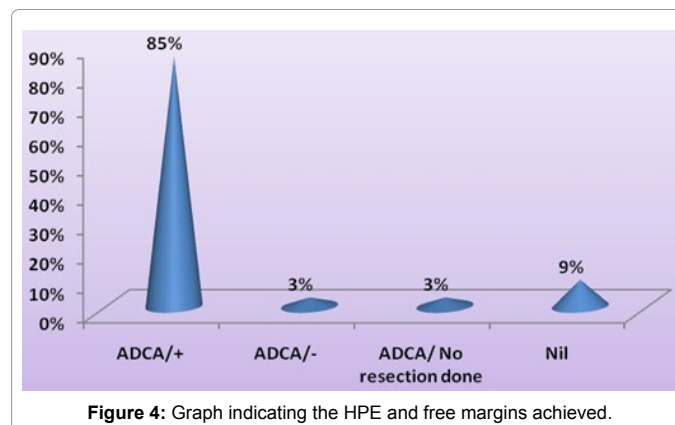
On analysing a study conducted by Bixu Wen [10] were it is shown that T stage decreased in 153 patients (72.9%), and increased in 5 (2.4%), and remained unchanged in 52 (24.8%); N stage decreased in 116 patients (55.2%), increased in 13 patients (6.2%), remained unchanged in 20 patients with clinically positive lymph nodes (9.5%) and 61 (29.0%) with clinically negative lymph nodes. After neoadjuvant CRT, postoperative pathological evaluation according to TNM classification showed T downstage in 153 patients (72.9%), N downstage in 116 patients (55.2%) and pathological TNM downstage in 132 patients (62.9%). In our study, it was found out that there was a reduction in both T and N staging following CRT in 91% and in 9% no down-staging was seen. There was a significant p-value of 0.02 percent in the present study.

From the analysis of the studies, it is inferred that preoperative CRT achieves significant down-staging which helps in better resection margins. In the present study, the better margins available for resection was seen to a distance of 7 cm with a p-value of 0.01 which falls well within the range of the distance (6-10 cm from anal verge) required to perform sphincter-saving procedures [11].

In a study conducted by Mark W et al. [12], the observation was made that out of 140 patients who received neoadjuvant CRT 46 patients underwent sphincter-preserving surgery LAR. In the present study, it is observed that out of 33 patients 19 underwent sphincter preserving LAR procedure and 8 AR were performed. In the present study, 3 patients underwent APR, APR with colostomy and palliative colostomy due to inability to achieve down-staging compared to Mark W et al. study in which 65 underwent APR and 3 APR+TAH, 2 underwent Hartmann's procedure and 1 wide excision. With respect to the statistics of present and this study quoted there is no similarity in the ability to perform a sphincter-saving procedure. The present study suggests that the ability to be able to perform a sphincter-saving surgery from which an opinion can be made that preoperative CRT is helpful to downstage cancer thereby allowing to perform a sphincter-preserving operation. 2 deaths were seen in the present series one which was due to toxicity post CRT and one due to causes unrelated to the study and was deemed insignificant. Following CRT and surgery, a negative margin was achieved in 28 patients and one patient had positive margin was seen needing postoperative RT.

The percentage of anastomotic leaks were higher in the study conducted by Paul et al. compared to the present study possibly due to a large sample size in the former (n=36315) [13].

In the follow-up period which was set for 3 months post-surgery was



carried out in which the patient was evaluated with DRE examination, serum CEA levels, USG abdomen and pelvis and colonoscopy (Figure 4).

It was found out that 87% of the patients did not have any growth. 6 percent of the patients which included 2 patients died before follow-up period. Preoperatively, a mean CEA level of 15.17 ± 13.34 and a reduction to level with a mean 1.59 ± 2.37 with a significant p-value of <0.001 which was statistically significant. 85% had no evidence of ascites or metastatic nodules in USG abdomen. In 6% no assessment was possible due to death of patient and 3 patients were lost to follow-up.

From this, it can be inferred that there was no evidence of recurrence or synchronous growths in the rectum and the patients in the present series had an uneventful follow-up period.

Conclusion

From the study, after analyzing the observations the following conclusions were made. Patients on subjection to Neoadjuvant chemoradiotherapy there was significant down-staging seen in the TNM stage in 91% of the patients with a p-value of 0.02 which was found to be statistically significant. There was a significant down staging in the tumor with a distance of 7.74 ± 1.55 cm with a p-value of 0.01 which was deemed significant and enabled us to perform sphincter-saving surgeries *viz.*, LAR and AR in 81% of the study population. The most common histological grade was adenocarcinoma of moderate grade which accounted for 76% of the patients and 85% had negative margins.

Summary

The patients when subjected to preoperative neoadjuvant CRT down-staging were achieved in 91% of the patients in the series. This allowed us to perform sphincter preserving surgeries as there was adequate down-staging with better margins of resection. Thus from this study a conclusion that preoperative neoadjuvant CRT is safe and effective to perform sphincter preserving surgeries in locally advanced carcinoma.

Conflict of interest

Authors have no conflict of interest to disclose.

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