ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

Original Research Article

Assessment of Oncological outcomes in Patients with Locally-Advanced Rectal Cancer Treated with Neoadjuvant Chemoradiation followed by Total Mesorectal Excision in a Tertiary Care Centre

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Received: 15-09-2024 / Revised: 31-09-2024 / Accepted: 17-11-2024

ABSTRACT

Background
Locally-advanced rectal cancer (LARC) differ from early rectal cancer in terms of requiring multimodal preoperative management. This strategy has been shown to achieve higher rates of locoregional control of disease and thereby improving overall and disease-free survival. Through this study, we try to analyse the oncological outcomes in locally-advanced rectal cancer treated with neoadjuvant chemoradiation (CRT) followed by total mesorectal excision (TME).

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
Thirty six patients were accrued for this study, of which, 23 (63.8%) were males and 13 (36.1%) females. Downstaging of tumor was noted in 75% of Stage II tumors, 100% of Stage III A tumors and 73.3% of Stage III B tumors and 85.7% of Stage III C tumors. Complete pathological response (ypT0N0) was noted in 4 (11.1%) patients, of which 2 were stage III B, 1 each of stages II A and III A. The mean overall survival in this study was observed to be 12.5months. The 3-year overall survival was 65% and recurrence-free survival was 82%. On multivariate analysis, only mesorectal fascia involvement was found to be associated with poor survival.

Conclusion

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Neoadjuvant concurrent chemoradiotherapy is an accepted modality of treatment for locoregionally-advanced rectal cancer, which offers higher rates of downstaging, TME and hence improved oncological outcomes.

Keywords: Locally-Advanced Rectal Cancer, Neoadjuvant Chemoradiation, Overall Survival, Recurrence-Free Survival, Prognostic Factor.

INTRODUCTION

Rectal cancer ranks eighth amongst the leading cancers worldwide accounting for about 729,833 (7.1%) new cases, and ranks sixth in India accounting for about 70,038 (5.0%) new cases.[1]

During the late 1970s, rates of pelvic recurrence ranged from 15 to 40% and 5-year overall survival rates of 30-69% was observed.[2] However, with the advent of multidisciplinary management options available for locally-advanced rectal cancer (LARC) there has been significant improvement in locoregional and systemic control of the disease and resultant improved survival.

Although surgical management remains the cornerstone in management of rectal cancer, upfront surgery alone in locally-advanced rectal cancer (LARC) results in higher rates of local recurrences.[3] To help mitigate this problem, multimodality treatments have been adopted.[4] While total mesorectal excision (TME) alone has shown to decrease local relapses up to 6%, with an estimated 5-year overall survival (OS) of about 75% and 10-year OS of 60%.[5,6] TME and neoadjuvant chemoradiation (CRT) combined have demonstrated exceedingly greater local control.[7-11] This study was undertaken to assess the oncological outcomes of LARC treated with neoadjuvant CRT followed by TME.

MATERIALS & METHODS

This is a prospective observational study undertaken in Karnataka Medical College and Research Institute (KMCRI) Hubballi from December 2019 to December 2021, consisting of 36 patients aged between 22 to 68 years, with histologically proven locally advanced adenocarcinoma of rectum, with a Karnofsky Performance Score (KPS) of 70 or more. Patients with stage I disease or distant metastases, uncontrolled comorbidities, prior onoclogical 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. Pretreatment 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 2mm 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) 400mg/m^2 IV bolus with Leucovorin 20mg/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. Surgery was performed 8-10 weeks after chemoradiation. the tumor along with the mesorectal

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lymph nodes were sent for histopathological examination (HPE), and pathological response was assessed, which was graded as complete response, partial response and no response.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%).. Student t-test (two-tailed, independent) is applied to determine the significance of study parameters on continuous scale between the groups on metric parameters. Chi-square / Fisher Exact test has been used to assess the significance of study parameters on categorical scale between two or more groups. 3-year overall survival (OS) and recurrence-free survival (RFS) have been calculated using Kaplan-Meier method and Cox regression analysis has been used for univariate and multivariate analysis of independent prognostic factors for survival outcomes. A p-value of <0.05 was considered statistically significant and SPSS v.27.0 (IBM Corp.^{TM}, Armonk, NY, USA) was used to perform statistical analysis.

RESULTS

Patients in the study group ranged from 22 years to 68 years, with a median age of 48.75±11.91 years, which comprised of 23 (63.8%) males and 13 (36.1%) females. 15 (41.7%) patients were known smokers. Mean body mass index (BMI) was 27.42±3.73 kg/m2. [Table 1] Mean length of tumor measured by colonoscopy was 6.2cm. 12 patients (66.7%) had raised serum Carcinoembryonic antigen (CEA) levels. Majority (18; 50.0%) of the patients had proximal rectal tumors, with mesorectal fascia involved in 14 (38.9%) patients. Only 5 (13.9%) patients presented with large bowel obstruction, whereas, none (0%) with perforation.

		Number	Percent
Patient data			
Age (in years)	<30	3	8.3
	30-40	6	16.7
	41-50	9	25.0
	>50	18	50.0
Gender	Male	23	63.8
	Female	13	36.1
History of smoking	Known smoker	21	58.3
	Non-smoker	15	41.7
BMI	<18.5	0	0
	18.5-24.9	9	25.0
	25.0-29.9	18	50.0
	>30.0	9	25.0
Investigations			
Haemoglobin	Anaemia	15	58.3
	Normal haemoglobin	21	41.7
S. Albumin	Hypoalbuminemia	14	38.9
	Normal albumin	22	61.1
S. CEA levels	Raised CEA	12	66.7
	Normal CEA	24	33.3
Tumor characteristics			

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Location of tumor	Proximal-third rectum	18	50.0
	Mid-third rectum	7	19.4
	Distal-third rectum	11	30.6
MRFinvolvement	MRF involved	14	38.9
	MRF not involved	22	61.1
Presentation			
Obstruction	Obstructed	5	13.9
	Not obstructed	31	86.1
Perforation	Perforated	0	0
	Not perforated	36	100

Table 1: Baseline characteristics

BMI body mass index, CEA carcinoembryonic antigen, MRF mesorectal fascia

The most common T stage at presentation (pre-nCRT) was T3 (18; 50%), and the most common

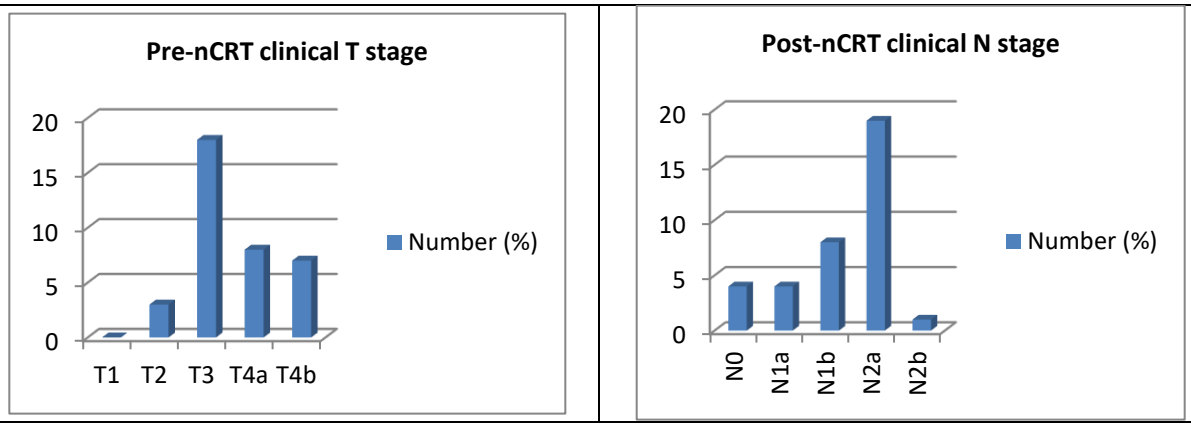

Figure 1: Pre-neoadjuvant chemroadiation T and N stage frequency distribution. nCRT neoadjuvant chemoradiation

N stage was N2a (19, 52.8%).[Fig 1]

Only 3 patients (8.3%) underwent emergency surgery, and 4 patients (11.1%) underwent laparoscopic surgery. Twenty five patients (69.4%) underwent anterior resection with covering stoma in 14 patients (38.9%). Mean operative time was 3.37 hours. Minor post-operative complications (i.e., surgical site infection SSI, urinary incontinence / retention, etc) were seen in 12 patients (33.3%) and major post-operative complications (i.e., wound dehiscence, anastomotic leak, etc) were seen in 9 patients (25.0%). Mean duration of hospital stay was 12.33±5.62 days.[Table 2]

Variables	No. of Patients	%
SURGERY:		
EMERGENCY/ELECTIVE		
• ELECTIVE	33	91.7
• EMERGENCY	3	8.3
• LAPAROSCOPIC SURGERY	4	11.1
• OPEN SURGERY	32	88.9

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SUGICAL PROCEDURE:		
• ANTERIOR RESECTION • ABDOMINOPERINEAL RESECTION WITH END COLOSTOMY • POSTERIOR PELVIC EXENTERATION	25 10 1	69.4 27.8 2.8
POST-OPERATIVE OUTCOMES:		
OPERATIVE TIME (hours)		
• <3.50 • >3.50	16 20	44.4 55.6
MINOR POST-OPERATIVE COMPLICATIONS		
• NIL • URINARY INCONTINENCE / RETENTION • SURGICAL SITE INFECTION	24 4 8	66.7 11.1 22.2
MAJOR POST-OPERATIVE COMPLICATIONS		
• NIL • WOUND DEHISCENCE • ANASTOMOTIC LEAK	27 3 6	75.0 8.3 16.7
DURATION OF HOSPITAL STAY (days)		
• <10 • 10-20 • >20	16 15 5	44.4 41.7 13.9

Table 2: Surgery and post-operative outcomes

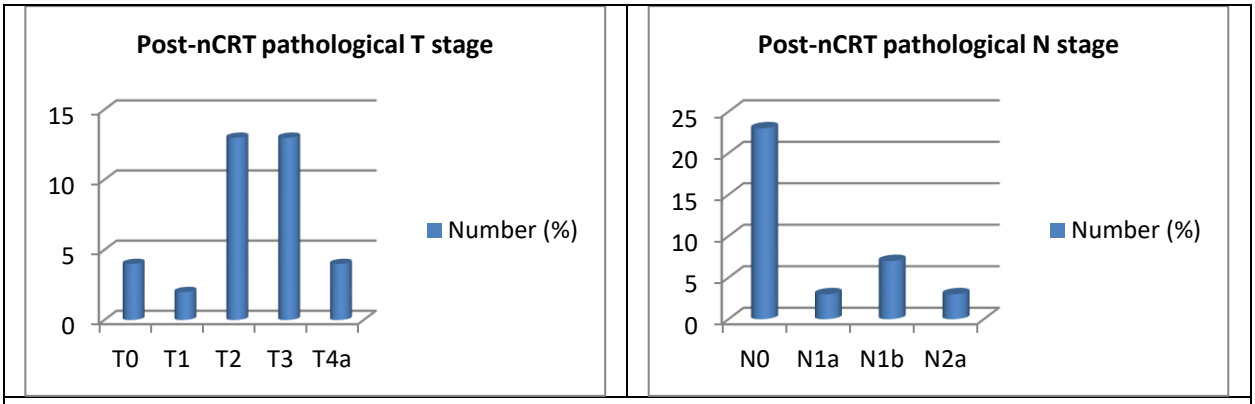

Figure 2: Post-neoadjuvant chemroadiation pathological T and N stage frequency distribution. nCRT neoadjuvant chemoradiation

Variables	**No.**	**%**
HISTOLOGY:		
• POORLY-DIFFERENTIATED ADENOCARCINOMA • MODERATELY-DIFFERENTIATED ADENOCARCINOMA • WELL-DIFFERENTIATED ADENOCARCINOMA	5 17 14	13.9 47.2 38.9
MARGINS		
• PROXIMAL AND DISTAL MARGIN NEGATIVE • PROXIMAL AND DISTAL MARGIN POSITIVE	36 0	100.0 0.0

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CIRCUMFERENTIAL MARGIN		
• CIRCUMFERENTIAL MARGIN NEGATIVE	32	88.9
• CIRCUMFERENTIAL MARGIN POSITIVE	4	11.1
LYMPHOVASCULAR INVASION		
• ABSENT LYMPHOVASCULAR INVASION	30	83.3
• LYMPHOVASCULAR INVASION +	6	16.7
PERINEURAL INVASION		
• ABSENT PERINEURAL INVASION	35	97.2
• PERINEURAL INVASION +	1	2.8

Table 3: Histopathological characteristics

The most common T stage post-nCRT was T2 and T3 (13, 36.1% each) and the most common N stage post-nCRT was N0 (23, 63.9%).[Fig 2] Final histopathological findings have been summarized in [Table 3]

Down staging of tumor was noted in 75% of Stage II tumors, 100% of Stage III A tumors and 73.3% of Stage III B tumors and 85.7% of Stage III C tumors.[Table 4, Table 5] Complete pathological response (ypT0N0) was noted in 4 (11.1%) patients, of which 2 were stage III B, 1 each of stages II A and III A.

Clinical Stage	PRE-nCRT Clinical Stage	POST-nCRT Pathological Stage	% Difference
0	0(0%)	4(11.1%)	11.1%
I	0(0%)	13(36.1%)	36.1%
II A	4(11.1%)	5(13.9%)	2.8%
II B	0(0%)	1(2.8%)	2.8%
III A	3(8.3%)	2(5.6%)	-2.7%
III B	15(41.7%)	9(25%)	-16.7%
III C	14(38.9%)	2(5.6%)	-33.3%
Total	36(100%)	36(100%)	-

Table 4: Pre-nCRT clinical and post-nCRT pathological stage frequency distribution

nCRT neoadjuvant chemoradiation

PRE-nCRT Clinical Stage	POST-nCRT Pathological Stage							Total
	0	I	II A	II B	III A	III B	III C	
II A	1(25%)	2(15.4%)	1(20%)	0(0%)	0(0%)	0(0%)	0(0%)	4(11.1%)
III A	1(25%)	2(15.4%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	3(8.3%)
III B	2(50%)	5(38.5%)	1(20%)	1(100%)	2(100%)	4(44.4%)	0(0%)	15(41.7%)
III C	0(0%)	4(30.8%)	3(60%)	0(0%)	0(0%)	5(55.6%)	2(100%)	14(38.9%)
Total	4(100%)	13(100%)	5(100%)	1(100%)	2(100%)	9(100%)	2(100%)	36(100%)

Table 5: Tumor downstaging distribution.

nCRT neoadjuvant chemoradiation, P=0.456, Not Significant, Fisher Exact Test

At the end of three years, 25 patients (69.44%) were alive at follow-up, 4 patients (11.11%) had local recurrence and 6 patients (16.66%) had distant metastases. The mean overall survival in this study was observed to be 12.5 months (95% CI; 10.4-14.62). The 3-year overall survival was 65%

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[Fig 3] and recurrence-free survival was 82%.[Fig 4] On multivariate analysis, only mesorectal fascia involvement was found to be associated with poor survival.[Table 6]

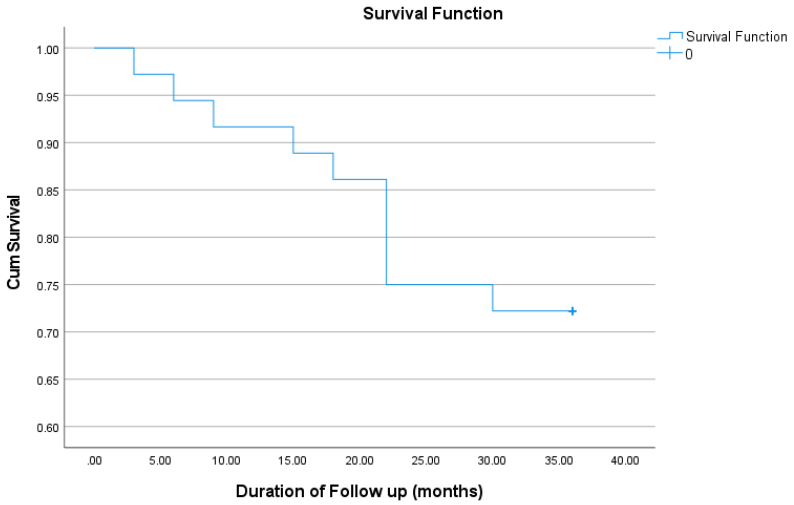

Figure 3: 3-year overall survival (OS) of 36patients with locally-advanced rectal cancer treated with neoadjuvant chemoradiation followed by total mesorectal excision

Time	5	10	15	20	25	30	35
Number at risk	34	33	32	29	27	26	26

Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
12.520	1.073	10.418	14.622	10.000	1.249	7.552	12.448
a. Estimation is limited to the largest survival time if it is censored.							

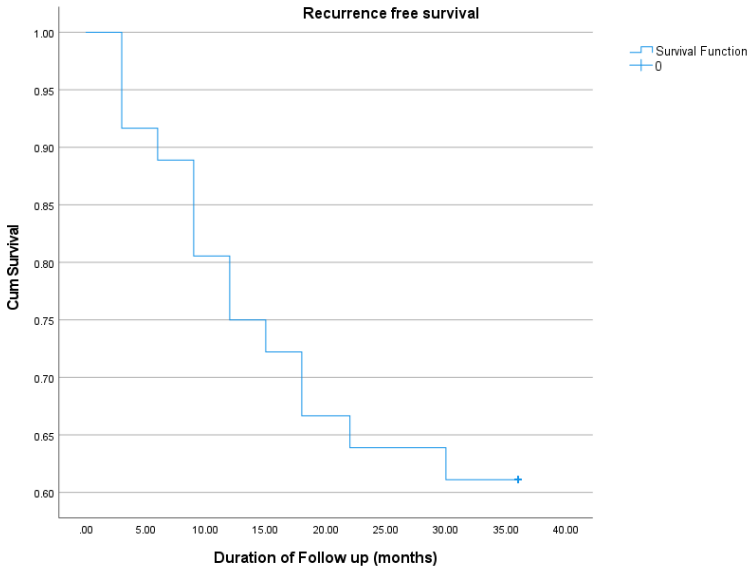

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Figure 4: 3-year recurrence-free survival (RFS) of 36patients with locally-advanced rectal cancer treated with neoadjuvant chemoradiation followed by total mesorectal excision

	Univariate Hazard Ratio				Multivariate Hazard ratio			
	Exp(B)	95.0% CI for Exp(B)		P Value	Exp(B)	95.0% CI for Exp(B)		P Value
		Lower	Upper			Lower	Upper	
	Ref.				Ref.			
Age	2.315	0.258	20.79	0.453	9.085	.280	295.272	0.214
Sex	1.569	0.443	5.561	0.485	.162	.008	3.348	0.239
Smoking	0.589	0.152	2.280	0.444	.152	.008	2.800	0.205
Comorbidities	1.80	0.50	6.35	0.362	2.935	.479	17.972	0.244
Anemia	1.020	0.288	3.61	0.976	.709	.125	4.013	0.697
Hypoalbuminemia	1.93	0.55	6.68	0.298	3.266	.355	30.065	0.296
CEA	0.855	0.221	3.31	0.821	.513	.090	2.925	0.452
Obstruction	2.12	0.450	10.04	0.341	.434	.012	16.074	0.650
MRF Involvement	3.13	0.88	11.13	0.078	5.685	.991	32.610	0.051

Table 6: Cox regression analysis of prognostic factors influencing OS and RFS

CEA carcinoembryonic antigen, *MRF* mesorectal fascia

DISCUSSION

Tumor response to neoadjuvant therapy is considered to be a valuable prognostic marker for LARC.[12] Clinical complete response (cCR) have been seen in up to 10-40% patients with LARC following neoadjuvant therapy, however, pathological complete response (pCR) rates are much lower.[13,14] Significantly lower local recurrences have been reported in patients who have shown pCR following neoadjuvant therapy, with 5-year recurrence-free survival rates of 90.5% in patients with complete response, 78.7% in those with intermediate response and 58.5% with poor response.[15] The argument for neoadjuvant chemoradiation in resectable rectal cancer is based on possibly downstaging tumors close to the circumferential resection margin or sphincter apparatus, hence enhancing R0 resection and sphincter preservation rates.

In our study stage 2 and 3 colorectal cancer patients were subjected to neoadjuvant chemoradiotherapy, following which, all patients underwent total mesorectal excision (TME). The INTERACT trial by Valentini V et al demonstrated a pathological complete response in up to 24% patients who received neoadjuvant chemoradiation.[16] Another trial, the ACCORD 12/0405-Prodige 2, demonstrated pathological complete response of 13.9% in patient group who received concurrent Capecitabine 800mg/m2 twice daily for five days per week, as opposed to 19.2% in those who received Capecitabine 800mg/m2 twice daily for five days per week along with weekly Oxaliplatin 50mg/m2.[17] On final histopathological reports in our study, downstaging of tumor was noted in 29 patients (80.55%), however complete pathological response was noted in only 4 patients (11.11%), which could be attributed to higher number of patients with advanced disease (higher baseline T and N stages) in our study population.

A pooled analysis of survival outcomes for those who attained pathological complete response (pCR) following neoadjuvant chemoradiation showed a 5-year OS of 87.6% and 76.4% in those with and without pCR respectively.[18] The German Rectal Cancer study group trial demonstrated an 5-year OS of 76% in preoperative-treatment group, with a 5-year DFS of 68%.[6]

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A 2024 study by Lee JH et al demonstrated a 3-year OS of 97.6% and 3-year intrapelvic recurrence-free survival (RFS) and distant metastases-free survival of 94.2% and 86.6% respectively in patients with LARC treated with nCRT followed by TME. However, on univariate and multivariate analysis, tumor location, clinical staging, lateral pelvic lymph node status, pretreatment CEA levels, pathological tumor response and boost were not found to be statistically significant independent prognostic factors.[19] However, the 3-year OS and RFS in our study was 65% and 82% respectively. Only MRF involvement was found to be statistically significant independent prognostic factor for survival. MRF involvement translates to higher risk of inadequate surgical clearance, thereby increasing the risk of local recurrence and distant metastasis by way of residual tumor and hence positive pathological circumferential margin (CRM).[20-22]

CONCLUSION

Neoadjuvant chemoradiation followed by total mesorectal excision for locally-advanced rectal cancer has shown to achieve comparable results by way of better compliance, improved local control of disease and acceptable oncological outcomes.

Ethical Approval

This study has been approved by the Institutional Ethics Committee.

Acknowledgements

Nil.

Conflicts of Interest

Nil.

Disclosures

Nil.

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