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Original Article

Implications of Neoadjuvant Chemoradiotherapy on Surgical Management of Locally Advanced Rectal Cancers

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Abstract

Background: Rectal cancer it accounts for over a third of mortality and morbidity worldwide in cancer cases. 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. Pre-operative chemo radiotherapy has better remission rates compared to stand-alone surgery. With the advantage of better local control, low toxicity rates and reducing local recurrence. The study was undertaken to evaluate the implications of neoadjuvant chemoradiotherapy (NACRT) on surgical management of locally advanced rectal cancers.

Methods: This was an observational, longitudinal study in Kashmir valley over period of 28 months where patients with locally advanced rectal cancers (stage 2 [cT3-4N0M0] and stage 3 [cT1-4N1-2M0]) were subjected to NACRT for over a period of 6–8 weeks and restaging was done in all patients after a gap of 6 weeks and all patients were assessed for radiological response and a down staging of tumor was assessed before surgery. After the surgical intervention, surgical specimen was sent for histopathological response of tumor.

Results: Total number of patients in a study was 34, the maximum patients between of age 51–60 year (38.2%) females outnumbered males. We analyzed the patients for pre NACRT staging and observed that almost (44.1%) were in T3N2M0 stage followed by (35.3%) in T4N2M0 staging and (20.6%) in T3N0M0 stage. After receiving NACRT it was observed that most of the patients constituting (50%) were in T3N0M0 stage followed by (26.5%) in T2N0M0 stage, (14.7%) were in T0N0M0 stage post therapy and only (8.8%) of patients remained unchanged. We noticed (79.4%) patients were in N2 and (20.6%) patients were in N0 in pre NACRT staging. After neo adjuvant (91.2%) were in N0 stage and only (8.8%) were in N2 which means almost (71%) down-staging in N2. We observed that no patient were in T0 and T2 staging and (64.7%) and (35.3%) were, respectively, in T3 and T4 staging before NACRT. We observed that most common procedure was LAR constituting about (38.2%) followed by ultra LAR and APR equally constituting (26.5%), the rarest procedure was inter sphintric constituting about (8.8%) of cases. We observed that (14.7%) patients showed complete response while as (76.5%) showed partial pathological response and (8.8%) patients did not respond to the treatment.

Conclusion: We observed a significant down-staging of TNM classification of patients who received NACRT. There was no progression of disease during the study period and the total down-staging in T was 61.8%, in N it was 88.9%.

Key words: Neoadjuvant chemoradiotherapy staging, Neoadjuvant chemotherapy, Rectal cancer, Chemoradiotherapy

INTRODUCTION

Rectal cancer is being increasingly observed in Indian population with increase in change in diet and lifestyle habits.[1] It accounts for over a third of mortality and morbidity worldwide in cancer cases.[2] Recent studies have shown that preoperative chemoradiotherapy 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, namely, (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]

Total mesorectal excision coupled with neoadjuvant chemo-radiotherapy is currently considered the standard treatment

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for patients with locally advanced rectal cancers (LARC). This multimodality treatment has resulted in improved local control rates, although showing no long-term survival benefits.[4-9] Various studies across literature have reported pathological downstaging and a complete pathological response rate (ypCR) of 15–27% following neoadjuvant chemoradiotherapy (NACTRT) before radical surgery.[10] This has translated into not only a superior and improved survival but also decreased locoregional and systemic recurrence. Rectal cancer accounts for 30% of all colorectal carcinoma. The use of preoperative radio chemo therapy has been used in treatment of rectal cancers for two decades and its use gradually increased especially in T3–T4 or N1-N2.[11,12] The strategy of performing preoperative instead of post-operative treatment has proven advantages of the lower acute toxicity,[13] lower total dose of radiation needed,[14] and eventually tumor regression and down staging to enable curative resection and even sphincter preservation.[15-18]

nCRT not only minimizes tumor size but goes along with the increasing tumor resection rate with a very minor side effect. nCRT is more effective than adjuvant therapy, it is associated with tumor down-staging and high rate of pathological complete response, down-staging pT and pN stage and fewer cases of venous, perineural, or lymphatic invasion, increased tumor resectability, reduction in local recurrence and decreasing toxicity.[5,19] Statistical multivariate analyses have confirmed that the response to nCRT was predictive of improved OS among the patients with locally advanced rectal cancer.[20,21]

Contrast-enhanced computed tomography abdominal pelvis and MRI pelvis was used for staging in pre and post neoadjuvant settings with MR used for loco-regional staging and the following TNM staging was used as follows.

Aims and Objectives

To evaluate the implications of NACRT on surgical management of locally advanced rectal cancers with respect to:

1. Down staging of tumor (primary and nodal)
2. Histopathological responses
3. Sphincter preservation

MATERIALS AND METHODS

This study was conducted in Postgraduate Department of General Surgery, Government Medical College Srinagar over a period of 29 months after obtaining ethical clearance from Institutional Ethical Committee.

Inclusion Criteria

The following criteria were included in the study:

- All histologically documented cases of rectal adenocarcinoma
- Locally advanced rectal cancers, that is, stage II (c T3-T4 N0 M0) and stage III (cT1 – T4 N1 – N2 M0)
- Any age group

Exclusion Criteria

The following criteria were excluded from the study:

- Stage-I rectal carcinoma
- Pregnancy
- Patients with distant metastasis
- Recurrent rectal carcinoma

Methodology

This was an observational, longitudinal study where patients with locally advanced rectal cancers were subjected to neo-adjuvant chemoradiotherapy for 25–28 cycles over a period of 6–8 weeks and restaging was done in all patients after a gap of 6 weeks and all patients were assessed for radiological, local response and a down staging of tumor was assessed before surgery. After the surgical intervention, surgical specimen was sent for histopathological response of tumor.

RESULTS

The maximum patients were between of age 51 and 60 years (38.2%) and the least number of patients belonged to < 30 years (11.8%). Females outnumbered males with 19 (55.9%) females against 15 patients (44.1%) males.

MRI down staging was taken as a standard to get the radiological response and we observed that (64.7%) and (35.3%) were in T3 and T4 staging before nCRT. However, post nCRT, we observed (50%) patients were in T3, (26.5%) in T1T2, (14.7%) T0 and (8.8%) T4 and eventually reduction of T grading was calculated. Total 22 patients were in T3 in Pre nCRT downgraded to T1T2 (7) patients and T0 (5) patients. Total 12 patients were in T4 in Pre nCRT downgraded to T3 (7) patients, T1T2 (2) patients, and 3 patients remained in T4. Hence, 61.8% downgrading was seen in T stage, clearly there was no progression of tumor staging in patients statistically significant. We noticed (79.4%) patients were in N2 and (20.6%) patients were in N0 in pre nCRT staging. After nCRT (91.2%) were in N0 stage and only (8.8%) were in N2, which means 24 out of 27 who were in N2 stage downgraded into N0 and which means almost (88.9%) downgrading in nodal staging. There was no progression of nodal staging with significant statistical difference.

Mesorectal fascia (MRF) involvement on MRI was taken one of the radiological modality to assess the response of nCRT. Out of 34 patients 16 patients had involvement of MRF (47.1%), rest of the patients were not involving the MRF. After receiving the neoadjuvant MRF involvement

was reassessed and following results were shown. Out of 16 patients, 12 patients had shown response which is nearly (75%) down staging, only four patients who did not show any down grading there was no progression of disease during the study period. We analyzed pre nCRT and post nCRT MRF involvement in association with histopathological MRF and observed that there is a significant difference between pre nCRT MRF and histopathological MRF involvement because out of 16 Pre nCRT MRF cases no one had histopathological MRF involvement. 16 patients were recorded with anal verge distance <4 cm and 18 patients were observed with anal verge distance >4 cm. There were 16 patients who fall in low rectal tumors distance from anal verge was <4 cm.

After receiving the nCRT tumor response for low rectal tumors was assessed on DRE and following findings were taken. There were three patients (18.8%) who had no palpable mass on DRE, 9 patients had tethered growth (56.3%) and 4 patients showed no response had fixed growth. Among 8 patients who had fixed growth, 4 changed into tethered growth, 4 remained unchanged. Among 8 patients who had tethered growth 3 patients showed complete response 5 remained unchanged. Total downstaging was 43.8%, there was no progression of disease during the study period. Pathological response of concurrent nCRT was taken from histopathological report of surgical specimen of a patient. Mandrad grading was used for pathological response, we observed that (14.7%) patients showed TRG1 (complete response), (76.5%) showed TRG2, TRG3, and TRG4 partial response, respectively. Only three patients out of 34 showed (TRG5) no response 8.8%.

Patients who have undergone APR have external sphincter involvement and intersphincteric space involvement (pre-nCRT). Out of 9 patients who underwent APR, in pre-nCRT 5 patients have T3N2M0, 3 patient have T4N2M0, and 1 patient had T3N0M0. Other factors were taken into consideration such as age, anal tone, surgeons choice, and patients consent. Three patients underwent intersphincteric resections, in pre-nCRT 1 patient was T3N0M0, 1 patient T4N2M0, and 1 patient T3N2M0. After nCRT 1 T3N0M0, another patient T1/T2 N0M0, 1 patient showed complete response T0N0M0 [Tables 1-4].

DISCUSSION

In this present study on implications of neo-adjuvant chemoradiotherapy on locally advanced rectal cancers, we observed that mean age of patients who qualified the inclusion criteria of the study was (47.8 ± 14.51) years. The maximum number of patients belonged to the age interval of (51–60) years. In the same kind of study, Laishram *et al.*[22] reported the maximum number of patients was in the age interval of (60–69) years and Ibrahim *et al.*[23] observed that maximum number of patients were below 40 years of age. However, Vinay and Vybhav[24] reported that most of the patients were in between (30 and 60) years of age. Out of the total of 34 patients included in the study we observe that almost (56%) were females and rest were males, similar kind of gender distribution was reported by Vinay and Vybhav[24] but contrary to this Laishram *et al.*[22] and Ibrahim *et al.*[23] reported that maximum number of cases were males. We analyzed the patients for pre nCRT staging and observed that almost (44.1%) were in T3N2M0 stage followed by (35.3%) in T4N2M0 staging and (20.6%) in T3N0M0 stage. All the patients who received the nCRT, clinical staging was done by local examination, colonoscopy/sigmoidoscopy and MRI pelvis was done. All the patients who have even complete response on imaging principally on MRI were operated. Surgery was done according to the local regional response, but final response of tumor was taken from histopathological specimen using TNM staging. After receiving nCRT it was observed that most of the patients constituting (50%) were in T3N0M0 stage followed by (26.5%) in T2N0M0 stage, (14.7%) were in T0N0M0 stage post therapy and only 3 patients remained unchanged constituting (8.8%) which was pre nCRT, clearly there was a down-staging in each stage post nCRT. In our study, we observed reduction in both T and N staging after nCRT, we noticed (79.4%) patients were in N2 and (20.6%) patients were in N0 in pre nCRT staging. After neoadjuvant (91.2%) was in N0 stage and only (8.8%) was in N2 which means almost (71%) down-staging in N2. There was no progression of nodal staging in any patient with a significant nodal response ($P < 0.001$). We also analyzed in our study that in pre nCRT there was no patient with T0 and T2 staging and (64.7%) and (35.3%) were, respectively, in T3 and T4 staging. However, post nCRT, we observed (14.7%) in T0, (26.5%) in T2, (50%) in T3, and (8.8%) were in T4 staging. Evidently, a reduction of (14.7%) in T3 stage and (18.2%) reduction in T4 stage after nCRT. Wen *et al.*[25] reported in their study that after nCRT, T stage decreased in almost (73%) of cases, increased in (2.4%) and remained unchanged in (24.8%); they also noticed that N stage also decreased in (55%), increased in (6.2%) cases and remained unchanged in 20 patients. In the same way, Vinay and Vybhav[24] observed a significant decrement in T and N staging after nCRT. Abdalla *et al.*[26] reported overall down-staging in (86.11%) in their study, similarly Rashid *et al.*[27] reported down staging in (56.7%) of cases while as a study from Duke's university revealed a down-staging in (82%) of cases almost compatible with our findings. We analyzed the distribution type of surgeries performed according to the local regional tumor status and distance of tumor from anal verge; we observed that most common

procedure was LAR constituting about (38.2%) followed by ultra LAR and APR equally constituting (26.5%), the rarest procedure was inter sphintric constituting about (8.8%) of cases. Gerard *et al.*[28] conducted a study on improved sphincter preservation in low rectal cancer with high dose of pre-operative radiotherapy and observed that most of the patients who underwent sphincter-preserving surgery for low rectal cancer have good post-operative sphincter function but almost (20%) will be more or less incontinent not only for flatus and loose stool but also for solid stool In a study conducted by Mark *et al.*,[29] observed that out of 140 patients who underwent for nCRT, 46 cases underwent sphincter-preserving surgery LAR. In a study conducted by Vinay and Vybhav,[24] it was observed that 19 out of 33 underwent sphincter preserving LAR procedure and 8 cases were reportedly performed by AR, 3 patients underwent APR. In our study, we analyzed the patients with respect to pathological response and observed that (14.7%) showed complete response while as (76.5%) showed partial pathological response, and (8.8%) patients did not respond to the treatment. In a study conducted by Yu *et al.*,[30] it was observed that out of 105 patients 13 (12.38%) almost similar to our observation. Dunst *et al.*[31] reported the (7%) complete response rate post neoadjuvant therapy while as in a similar kind of study by Rashid *et al.*[27] (3.3%) complete response rate was observed. However, in another likewise study by Sinukumar *et al.*[32] (61%) complete pathological response was observed. Some studies have reported an improved in survival rate[22,33,34] in patients with pathological down staging and post-operative chemotherapy while others are of the opinion that adjuvant chemotherapy be administered only in residual nodal disease patients.[35]

The present study investigated the effect of nCRT in terms of MRF involvement using magnetic resonance induction (MRI). Even though MRI is known to be highly accurate in predicting the involvement of the MRF at primary staging[36,37] but the assessment on post nCRT is more difficult because of the presence of fibrosis. We observed that 16 patients constituting (47.1%) had MRF involvement before nCRT. However, post nCRT it reduced to about (75%), that is, 11 out of 16 showed no MRF involvement and interestingly there was a strong statistical significant difference between pre nCRT MRF involvement and histopathological MRF involvement because out of 16 Pre nCRT MRF cases no one had histopathological MRF involvement. Only around (11.8%) did not show down grading. In a study conducted by Syed Nadeem *et al.*,[38] it was observed on initial staging MRI examination that eight out of 64 patients had advanced T3 tumors with a tumor close to the MRF, 31 had T3 tumors with MRF invasion, and 25 patients had T4 tumors (organ invasion). We compared pre nCRT involvement with histopathological MRF involvement and observed that there is a strong

Table 1 : Patient characteristics

Patient characteristics	Number of patients (%)
Age (years)	
≤30	4 (11.8)
31–40	7 (20.6)
41–50	5 (14.7)
51–60	13 (38.2)
>60	5 (14.7)
Mean±SD (range)	47.8±14.51 (24–80)
Gender	
Male	15 (44.1)
Female	19 (55.9)
Pre-nCRT staging	
T3N0M0	7 (20.6)
T3N2M0	15 (44.1)
T4N2M0	12 (35.3)
Post-nCRT staging	
T0N0M0	5 (14.7)
T1/T2N0M0	9 (26.5)
T3N0M0	17 (50.0)
T4N2M0	3 (8.8)

SD: Standard deviation, nCRT: Neoadjuvant chemoradiotherapy

Table 2: Comparison based on T-staging and nodal staging before and after nCRT

Patient characteristics	Pre nCRT, *n* (%)	Post nCRT, *n* (%)	*P*
T-staging			
T0	0	5 (14.7)	0.002*
T1/T2	0	9 (26.5)	
T3	22 (64.7)	17 (50.0)	
T4	12 (35.3)	3 (8.8)	
Nodal staging			
N0	7 (20.6)	31 (91.2)	<0.001*
N2	27 (79.4)	3 (8.8)	

nCRT: Neoadjuvant chemoradiotherapy

Table 3: Mesorectal fascia involvement; pre-nCRT, post-nCRT, and histopathology

MRF involvement	Pre-nCRT, *n* (%)	Post-nCRT, *n* (%)	Histopathological MRF involvement, *n* (%)
Yes	16 (47.1)	4 (11.8)	0
No	18 (52.9)	30 (88.2)	34 (100)
Total	34 (100)	34 (100)	34 (100)
P	Pre-nCRT MRF involvement versus histopathological MRF involvement <0.001 (statistically significant)		

MRF: Mesorectal fascia, nCRT: Neoadjuvant chemoradiotherapy

Table 4: Pathological response and type of surgery

Patient characteristics	Number of patients (%)
Pathological response	
Complete response	5 (14.7)
Partial response	26 (76.5)
No response	3 (8.8)
Type of surgery	
Ultra LAR	9 (26.5)
LAR	13 (38.2)
APR	9 (26.5)
Inter sphinteric	3 (8.8)

LAR: Low anterior resection, APR: Abdomino-perineal resection

statistical significant difference between pre nCRT MRF and histopathological MRF involvement because out of 16 Pre nCRT MRF cases no one had histopathological MRF involvement.

In the current study, we observed that around (47.10%) had low rectal tumor distance (<4 cm) from anal verge and rest had >4 cm. Before subjecting patients for neoadjuvant, we performed DRE in all patients and it was observed that (50%) of patients had fixed growth while as (50%) had tethered growth. On post nCRT, tumor response for low rectal tumors was assessed on DRE whereby we observed that (18.8%) had no palpable mass, (56.3%) had tethered growth, and rest (25%) had fixed growth. Overall, there was (43.8%) down staging and no progression of disease was observed during the study period. In a similar kind of study due to Vinay and Vybhav,[24] patients were evaluated with respect to any novel growth on DRE, it was observed that around (87%) patients did not had any growth and (6%) of patients including two (02) patients died during the 3 months follow-up period. They reported that in one patient, there was no change in the preoperative period and mass was felt per rectum on examination.

CONCLUSION

In the present study, we observed a significant down-staging of TNM classification of patients who received nCRT. Due to this significant response we performed various types of surgeries and then evaluated the pathological responses. The most common pathological response was partial response constituting 77% followed by 15% with complete response. There was no progression of disease during the study period and the total down-staging in T was 61.8%, in N it was 88.9% (radiological response on MRI).

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