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Original Research Article

Post Total Neoadjuvant Therapy - Pathological Complete Response Among Individuals with Locally Advanced Rectal Adenocarcinoma in a Selected Tertiary Care Center, South India - A Follow-up Study

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Abstract:

Introduction: Total Neoadjuvant therapy (TNT), an emerging treatment strategy, involves the administration of systemic chemotherapy before and after chemoradio therapy, with the goal of maximizing tumor response and enhancing long-term outcomes. This research article aims to investigate the incidence of pCR following TNT among patients with locally advanced rectal adenocarcinoma at a tertiary care center in South India.

Methodology: This is a Prospective follow-up study conducted at a tertiary care center in the city of Chennai, South India between January 2019 and December 2022. After obtaining informed consent from eligible study participants, the investigator collected the sociodemographic and clinical profile information on demographics, tumor characteristics, treatment details, and follow-up outcomes of the study participants. Data collected was entered in Epidata version 3.1, while the data analysis was carried out using STATA version 12.0. Logistic regression analysis was used to identify potential predictors of pCR, including patient demographics, tumor characteristics, and treatment complications. Chi square test was used to assess the significance among categorical variables. P-value less than 0.05 was considered to be statistically significant.

Results: Out of 55 participants in the current study, 30.9% were females. Pathological Complete Response (pCR) was seen in 21.8% of study population. The most common presenting symptom was Bleeding per rectum (63.6%) followed by tenesmus seen among 20% of the study participants. Nearly every second female study participant had mid rectum as the site of adenocarcinoma and more than 90% of female study participants had moderately differentiated adenocarcinoma. Around two out of five study participants with hypertension alone as comorbidity was seen among females, while more than half of the study participants (57.14%) with both diabetes and hypertension as comorbidity were reported among males and it was found to be statistically significant ($p = 0.014$).

Conclusion: The present study provides important insights into the effectiveness of TNT in the treatment of locally advanced rectal adenocarcinoma. Our findings demonstrate that TNT is provides better pCR and support the incorporation of TNT as a standard treatment approach in locally advanced rectal adenocarcinoma.

Keywords: Pathologic complete response (pCR), Prospective study, Rectal Carcinoma, Total neoadjuvant therapy (TNT).

Introduction

Locally advanced rectal adenocarcinoma remains a significant clinical challenge, requiring a multimodal treatment approach to achieve optimal outcomes. Neoadjuvant therapy, including chemoradiotherapy, is preferably used in the management of locally advanced rectal cancer, as it facilitates tumor downstaging, improves local control, and raises the possibility of attaining a pathological complete response (pCR). [1, 2] Traditionally, the standard approach involved administering neoadjuvant chemoradiotherapy followed by surgery and adjuvant therapy as necessary. Total Neoadjuvant Therapy (TNT), on the other hand, aims to optimise treatment sequencing by administering systemic chemotherapy first, enabling the early

eradication of micrometastatic disease and increasing the possibility of attaining a complete response. This strategy has gained traction due to accumulating evidence supporting its efficacy and feasibility. [3]

With the aim of optimising tumour response and improving long-term results, total neoadjuvant therapy (TNT), an emerging treatment technique, involves the administration of systemic chemotherapy before and after chemoradiotherapy. (3, 4) TNT offers several potential advantages over conventional treatment strategies. By initiating systemic chemotherapy before surgery, TNT enables the identification of patients who may exhibit an exceptional response, allowing for tailored management plans. [4] Moreover, this approach offers the opportunity to downsize the tumor, facilitating sphincter-preserving surgeries and reducing the need for permanent colostomies. Additionally, administering systemic therapy early in the treatment trajectory may help address micrometastatic disease, potentially improving distant metastasis-free survival.

In comparison to traditional neoadjuvant therapy, TNT has demonstrated encouraging outcomes in terms of raising pCR rates and lowering the risk of disease recurrence. [5, 6] However, the incidence of pCR following TNT among Indian patients with locally advanced rectal adenocarcinoma remains poorly understood.

The idea of obtaining pCR, which is defined as the absence of residual tumour cells in the surgical specimen after therapy, has drawn a lot of attention as an alternative endpoint for better oncological outcomes. [3] Patients who achieve pCR have demonstrated superior disease-free survival, reduced risk of distant metastasis, and improved overall survival rates [7,8]. Therefore, understanding the incidence of pCR following TNT and identifying predictors associated with treatment response are essential for optimizing therapeutic strategies and tailoring interventions for Indian patients. Assessing the incidence of pCR following TNT will provide valuable insights into the efficacy of this treatment approach and its potential impact on long-term outcomes. Furthermore, the goal of discovering treatment response predictors is to help guide treatment decisions, optimise patient selection for TNT, and improve individualised therapeutic methods for locally advanced rectal adenocarcinoma in Indian setting. This research article aims to investigate the incidence of pCR following TNT among patients with locally advanced rectal adenocarcinoma at a tertiary care center in South India.

Methodology

Study Design and Participants

This is a Prospective follow-up study conducted at a tertiary care center in the city of Chennai, South India. Lying in the heart of the city of Chennai, which in itself one of the most populous metropolitan cities in the country, this established tertiary care institution receives patients not only from the city of Chennai, but from across the states of South India. We included all adult patients diagnosed with locally advanced rectal adenocarcinoma who underwent TNT with curative intent between January 2019 and December 2022. Locally advanced rectal cancer was defined as T3 or T4 disease, staged according to AJCC 8th edition with or without nodal involvement on pretreatment imaging. Exclusion criteria included patients with incomplete data.

Since not much literature has been published on pCR in rectal adenocarcinoma, all the cases satisfying the eligibility criteria attending the medical oncology OPD of the Government Kilpauk Medical College, Chennai during the study period were included in the study. Based on expert opinion, considering the average number of cases visiting the oncology OPD in the last three years to be 50, the sample size for the current study was considered to be 55 patients with locally advanced rectal carcinoma with attrition rate of 10%.

Data Collection

After obtaining informed consent from eligible study participants, the investigator collected the sociodemographic and clinical profile information on demographics, tumor characteristics, treatment details, and follow-up outcomes of the study participants. Tumor characteristics included tumor stage, location, and histology. Treatment included the Concurrent chemoradiation (CCRT) using tab. Capecitabine (825mg/m2) twice daily on radiation days, Consolidation chemotherapy (CC) with CAPOX/FOLFOX4 regimen for six cycles after completion of CCRT. All patients received a long course of radiotherapy with dose of 50.4Gy in 28 daily fractions. This was followed by surgery at an interval of 3-4 weeks after completion of CC. Follow-up outcomes included the incidence of pCR and complications such as Hand Foot syndrome (NCI-CTCAE grading) and diarrhea (NCI-CTCAE grading). [9]

Definition of Pathological Complete Response

We defined pCR as the absence of any residual invasive tumor in the surgical specimen and lymph nodes, as confirmed by pathological examination. We used a standardized definition of pCR based on the guidelines of the College of American Pathologists and the National Comprehensive Cancer Network. [8, 9]

Statistical Analysis

Data collected was entered in Epidata version 3.1, while the data analysis was carried out using STATA version 12.0. [10, 11] Descriptive statistics were used to summarize the sociodemographic and clincal profile of the study population. The primary outcome of interest was the incidence of pCR. Continuous variables were summarized as mean (SD), while categorical variables were summarized as frequency (proportions).

We used logistic regression analysis to identify potential predictors of pCR, including patient demographics, tumor characteristics, and treatment complications. Chi square test was used to assess the significance among categorical variables. P-value less than 0.05 was considered to be statistically significant.

Ethical Considerations

This study was approved by the Institutional Review Board of the study center. Informed written consent was obtained from all participating patients prior to the study.

Results

Out of 55 participants in the current study, 30.9% were females. pCR was seen in 21.8% of study population. The overall mean (SD) age of the study participants was 57.05 (10.77) years, while the mean (SD) age of male study participants was 56.24 (11.37) years. Study participants of age group more than 60 years of age contributed for more than 40% in the current study. 11 (20%) of the study participants belonged to age group of less than 45 years. (Table 1) more the 40% of the study participants did not have any comorbidities (41.8%), while 32.7% study participants had both diabetes and systemic hypertension as their comorbidities.

Table 1: Age wise distribution of cases among the study participants (N=55)

Age (in years)	n (%)
<45	11 (20)
45 – 60	21 (38.18)
> 60	23 (41.82)

The most common presenting symptom was Bleeding per rectum (63.6%) followed by tenesmus seen among 20% of the study participants. Nearly every second female study participant had mid rectum as the site of adenocarcinoma and more than 90% of female study participants had moderately differentiated adenocarcinoma. More than 9 out of 10 female study participants witnessed downstaging of tumour after Total Neoadjuvant therapy. Grade III – IV HFS (NCI grading) was seen in more than 25% of the study participants, while One out of every ten study participants reported Grade – IV diarrhea (CTCAE grading). Nearly 80% of the study participants completed their full treatment, while 9.1% and 10.9% of study participants missed one and two cycles of treatment respectively.

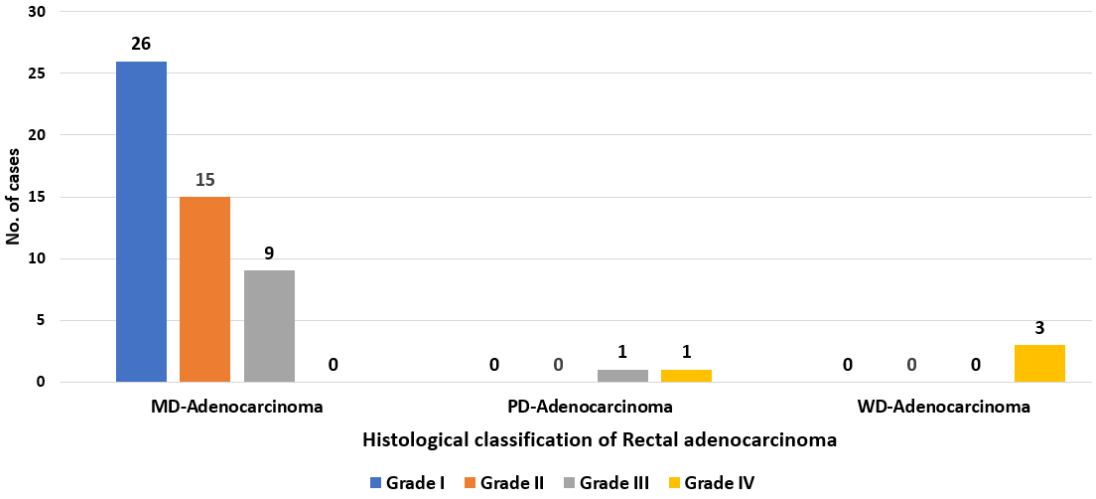

Figure 1: Distribution of histological classification of rectal adenocarcinoma among the participants in the current study (N=55)

One out of every five study participants had sphincter involvement. Sphincter preservation was carried out in nine out of eleven participants with sphincter involvement. Only 3 participants with well differentiated adenocarcinoma reported Grade – IV Hand Foot Syndrome (HFS) according to NCI grading. (Figure 1)

Table 2: Association between sociodemographic and clinical profile with pathological complete response (pCR) among the study participants (N=55)

	Pathological Complete Response (pCR)									
	No, n(%)		**Yes, n(%)**		**Total, n(%)**		**OR**	**(95% CI)**	**P - value**
Gender									
Female	11	(64.71)	6	(35.29)	17	(100)	Ref	-	0.105
Male	32	(84.21)	6	(15.79)	38	(100)	2.90	(0.77,10.92)	
Presenting symptoms									
Bleeding PR	30	(85.71)	5	(14.29)	35	(100)	Ref	-	0.130
Constipation	3	(75)	1	(25)	4	(100)	2	(0.17,23.25)	
Perianal pain	2	(40)	3	(60)	5	(100)	9	(1.18,68.13)	
Tenesmus	8	(72.73)	3	(27.27)	11	(100)	2.25	(0.44,11.48)	
Comorbidity									
Nil	21	(91.3)	2	(8.7)	23	(100)	Ref	-	0.005
DM	6	(85.71)	1	(14.29)	7	(100)	1.75	(0.13,22.77)	
SHT	7	(100)	0	(0)	7	(100)	1	-	
DM, SHT	9	(50)	9	(50)	18	(100)	10.5	(1.88,58.61)	
RECTUM-SITE									
Lower	16	(100)	0	(0)	16	(100)	Ref	-	0.016
Mid	20	(64.52)	11	(35.48)	31	(100)	3.85	(0.41,35.47)	
Upper	7	(87.5)	1	(12.5)	8	(100)	1	-	
Histology									
MD - Adenocarcinoma	2	(66.67)	1	(33.33)	3	(100)	Ref	-	0.673
PD - Adenocarcinoma	39	(78)	11	(22)	50	(100)	0.56	(0.04,6.81)	
WD - Adenocarcinoma	2	(100)	0	(0)	2	(100)	1	-	
Pre Rx-Stage									
T3N0M0	5	(50)	5	(50)	10	(100)	Ref	-	0.109
T3N1M0	7	(77.78)	2	(22.22)	9	(100)	0.28	(0.03,2.11)	
T3N2M0	8	(100)	0	(0)	8	(100)	1	-	
T4N0M0	7	(70)	3	(30)	10	(100)	0.42	(0.06,2.68)	
T4N1M0	11	(84.62)	2	(15.38)	13	(100)	0.18	(0.02,1.27)	
T4N2M0	5	(100)	0	(0)	5	(100)	1	-	
Pre Rx-Stage (based on T)									
T3NxMx	20	(74.07)	7	(25.93)	27	(100)	Ref	-	0.346
T4NxMx	23	(82.14)	5	(17.86)	28	(100)	0.62	(0.17,2.26)	
HFS-NCI Grading									
Grade I	17	(65.38)	9	(34.62)	26	(100)	Ref	-	0.114
Grade II	13	(86.67)	2	(13.33)	15	(100)	0.29	(0.05,1.58)	
Grade III	10	(100)	0	(0)	10	(100)	1	-	
Grade IV	3	(75)	1	(25)	4	(100)	0.62	(0.05,6.96)	
CTCAE Diarrhoea Grading									
Grade I	17	(68)	8	(32)	25	(100)	Ref	-	0.137
Grade II	12	(100)	0	(0)	12	(100)	1	-	

Grade III	10	(83.33)	2	(16.67)	12	(100)	0.42	(0.07,2.40)	
Grade IV	4	(66.67)	2	(33.33)	6	(100)	1.06	(0.15,7.06)	
Downgrading									
Same stage	2	(100)	0	(0)	2	(100)	Ref	-	0.608
Downgrade	41	(77.36)	12	(22.64)	53	(100)	-	-	
Sphincter involved									
No	36	(81.82)	8	(18.18)	44	(100)	Ref	-	0.182
Yes	7	(63.64)	4	(36.36)	11	(100)	2.57	(0.60,10.93)	

Table 2 shows the pathological complete response of the study participants in association with sociodemographic and clinical profile. Pathological Complete Response was seen in more than 35% of female study participants. Comorbidities (p = 0.005) and site of rectal adenocarcinoma (p = 0.016) showed significant association with pCR among the participants in the current study. Histologically, none of the study participants with well differentiated adenocarcinoma were found to show pathological complete response, while only 22% of the cases with poorly differentiated adenocarcinoma showed pathological complete response and it was not found to be statistically significant (p = 0.673). (Table 2).

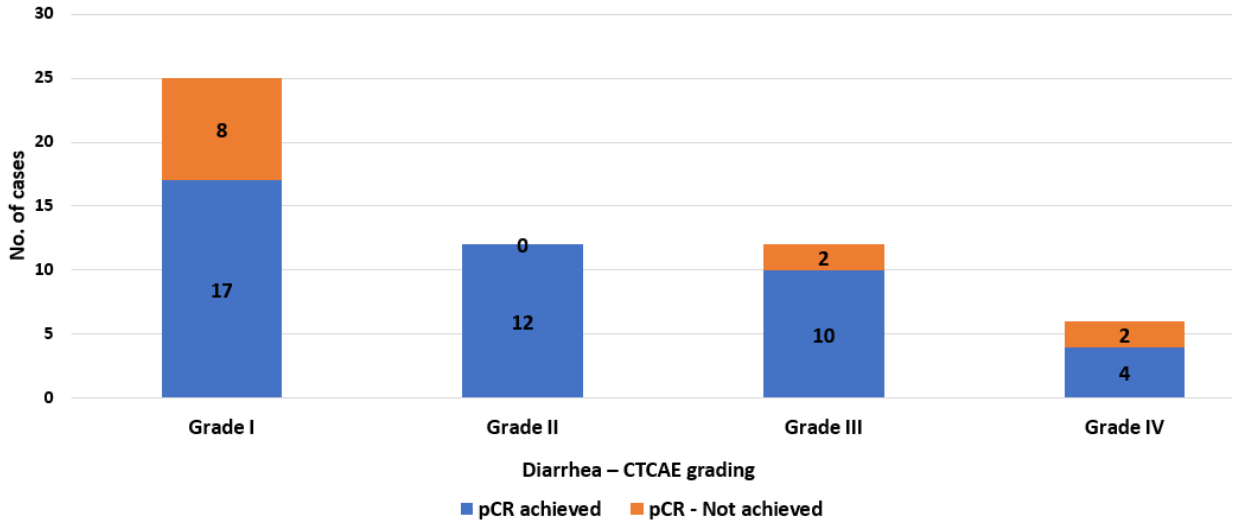

Figure 2: Distribution of Diarrhea - CTCAE Grading among the cases of rectal adenocarcinoma in the current study (N=55)

Down staging of rectal adenocarcinoma after total neoadjuvant therapy was noted in 25.93% and 17.86% study participants with pretreatment staging of T3NxMx and T4NxMx respectively. None of the study participants with Grade III HFS (NCI grading) reported pathological complete response, while 34.62% of study participants with Grade II HFS showed pathological complete response. (Table 2) Similarly, none of the study participants with Grade II CTACAE diarrhea reported to have pathological complete response after total neoadjuvant therapy, (Figure 2) while 32% of study participants with Grade I CTCAE diarrhea showed pathological complete response which was not found to be statistically significant (p = 0.137). (Table 2).

Table 3: Association between sociodemographic and clinical profile with gender among the study participants (N=55)

	Gender						**OR**	**(95% CI)**	**P - value**
	Male, n(%)		**Female, n(%)**		**Total, n(%)**				
Presenting symptoms									
Bleeding PR	25	(71.43)	10	(28.57)	35	(100)	Ref	-	0.169
Constipation	4	(100)	0	(0)	4	(100)	1	-	

Perianal pain	4	(80)	1	(20)	5	(100)	0.62	(0.06,6.30)	
Tenesmus	5	(45.45)	6	(54.55)	11	(100)	3	(0.74,12.10)	
Comorbidity									
Nil	19	(82.61)	4	(17.39)	23	(100)	Ref	-	0.014
DM	7	(100)	0	(0)	7	(100)	1	-	
SHT	4	(57.14)	30	(42.86)	7	(100)	3.56	(0.56,22.54)	
DM, SHT	8	(44.44)	10	(55.56)	18	(100)	5.94	(1.42, 24.65)	
RECTUM-SITE									
Lower	11	(68.75)	5	(31.25)	16	(100)	Ref	-	0.418
Mid	23	(74.19)	11	(25.81)	31	(100)	0.76	(0.20,2.88)	
Upper	4	(50)	4	(50)	8	(100)	2.2	(0.38,12.57)	
Histology									
MD - Adenocarcinoma	2	(66.67)	1	(33.33)	3	(100)	Ref	-	0.628
PD – Adenocarcinoma	34	(68)	16	(32)	50	(100)	0.94	(0.08,11.16)	
WD - Adenocarcinoma	2	(100)	0	(0)	2	(100)	1	-	
Pre Rx Stage									
T3N0M0	8	(80)	2	(20)	10	(100)	Ref	-	0.423
T3N1M0	5	(55.56)	4	(44.44)	9	(100)	0.32	(0.42,24.41)	
T3N2M0	5	(62.50)	3	(37.50)	8	(100)	2.4	(0.29,19.78)	
T4N0M0	5	(50)	5	(50)	10	(100)	4	(0.55,29.10)	
T4N1M0	11	(84.62)	2	(15.38)	13	(100)	0.73	(0.08,6.31)	
T4N2M0	4	(80)	1	(20)	5	(100)	1	(0.07,14.64)	
Pre Rx Stage (based on T)									
T3NxMx	18	(66.67)	9	(33.33)	27	(100)	Ref	-	0.464*
T4NxMx	20	(71.43)	8	(28.57)	28	(100)	0.80	(0.25,2.51)	
HFS-NCI Grading									
Grade I	17	(65.38)	9	(34.62)	26	(100)	Ref	-	0.842
Grade II	10	(66.67)	5	(33.33)	15	(100)	0.94	(0.24,3.62)	
Grade III	8	(80)	2	(20)	10	(100)	0.47	(0.08,2.71)	
Grade IV	3	(75)	1	(25)	4	(100)	0.63	(0.05,6.96)	
CTCAE Diarrhoea Grading									
Grade I	18	(72)	7	(28)	25	(100)	Ref	-	0.405
Grade II	10	(83.33)	2	(16.67)	12	(100)	0.51	(0.08,2.96)	
Grade III	7	(58.33)	5	(41.67)	12	(100)	1.83	(0.43,7.77)	
Grade IV	3	(50.00)	3	(50.00)	6	(100)	2.57	(0.42,15.92)	
Downgrading									
Same stage	1	(50)	1	(50)	2	(100)	Ref	-	0.527*
Downgrade	37	(69.81)	16	(30.91)	53	(100)	0.43	(0.02,7.35)	
Sphincter involved									
No	29	(65.91)	15	(34.09)	44	(100)	Ref	-	0.263*
Yes	9	(81.82)	2	(30.91)	11	(100)	0.43	(0.08,2.25)	

Table 3 shows the association of sociodemographic and clinical profile with gender of the study participants. More than 50% of the study participants with tenesmus as presenting symptom were females, but was not found to be statistically significant (p = 0.169). 3 out of 38 male participants and 1 out of 17 female participants in the current study reported HFS Grade – IV according to NCI grading. (Figure 3)

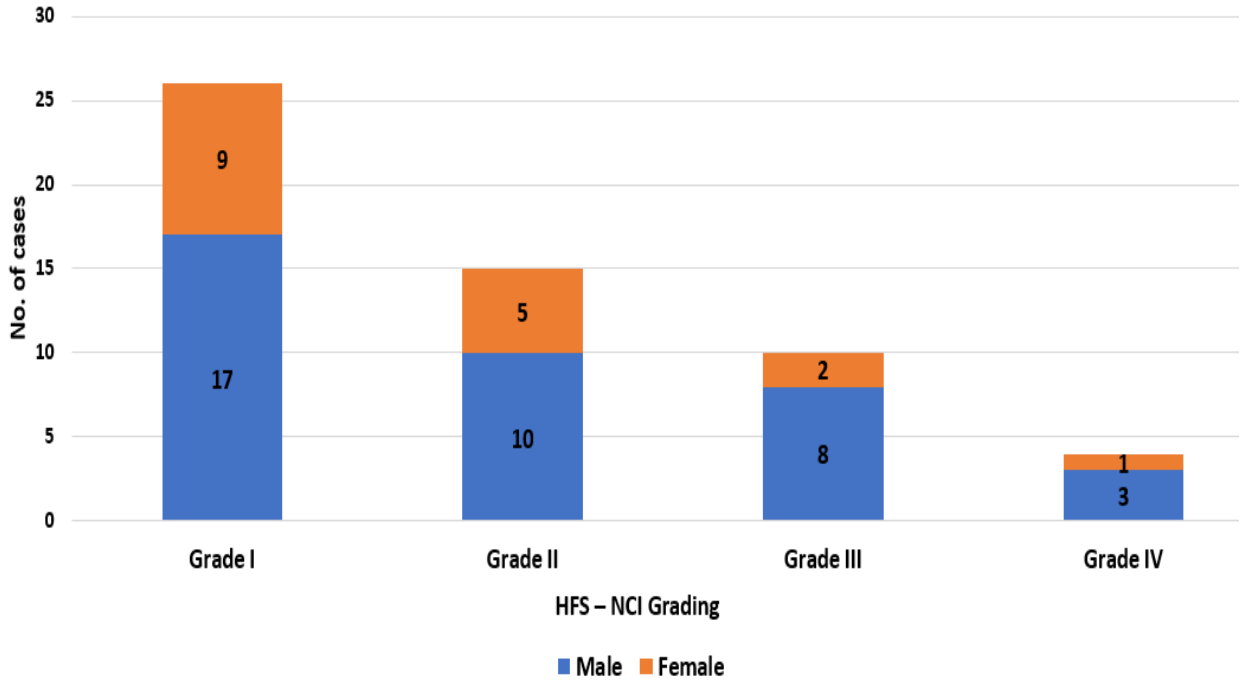

Figure 3: Distribution of HFS (NCI – Grading) among the cases of rectal adenocarcinoma in the current study (N=55)

Around two out of five study participants with hypertension alone as comorbidity was seen among females, while more than half of the study participants (57.14%) with both diabetes and hypertension as comorbidity were reported among males and it was found to be statistically significant (p = 0.014). (Table 3) 31.25% and 25.81% of study participants with location of carcinoma as lower and mid rectum were found among the females, while upper rectum as site of adenocarcinoma was equal (50%) among both the gender but was not found to be statistically significant (p = 0.418). Downstaging (69.81%) and sphincter involvement (81.82%) was more predominant among the males but were not found to be statistically significant. (Table 3)

Discussion

The purpose of our study was to evaluate the incidence of pathological complete response (pCR) among patients diagnosed with locally advanced rectal adenocarcinoma who were treated with total neoadjuvant therapy (TNT) with curative intent. Our study found that the incidence of pCR was 21.8%. On comparison with previously published studies, the incidence obtained in the present study was similar with that of findings obtained by Schou et al.[12] It was also observed that thepCR obtained in the current study was significantly higher when compared with a study conducted by Fernandez- Martos et al- that reported a pCR of 14.3% among their study population. (13) Similarly, lower pCR rate (19.5%) was documented in a study conducted by Gollins et al in 2020 when compared with the results of the current study. [3]

Studies conducted by Bujiko et al (Polish II trail), PORDIGE study by Conroy et al,Zhu et al, and Garcia-Aguilar et al reported pCR of 12%, 12%, 17% and respectively 18% which is lower than the results obtained from the current study. [14-17] Several studies which reported pCRafter TNT such as CONTRE study by Perez et al, AVACROSS study Nogueby et al Gao et al showed pCR of 33%, 34% and 36% respectively which is higher on comparison with the pCR obtained during the current study. [18 – 20] Reasons behind such wide differences across studies need to be explored, while study participants across studies vary broadly on region, ethnicity and dietary behaviours can be considered for such differences elicited across study groups.

The study participants in the present study had an overall mean (SD) age of 57.05 (10.77) years, which is comparable with the results of the Brazilian study conducted by Kim et al. (21)Moreover, the mean (SD) age was very much lower when compared to the Polish study conducted by Bujiko et al which reported 62(6) years. [14] Bahadoer RR et al reported Grade 3-4 diarrhea in 14.5% of their study population which is lower when compared to the results of the current study (32.7%). [22] This might be due to the

region-specific differences across the globe. Similar proportions of diarrhea such as 6.9%were reported on comparison with a Dutch study conducted by Peeters et al. [23]

One of the strengths of our study is the use of a standardized definition of pCR based on the guidelines of the College of American Pathologists and the National Comprehensive Cancer Network. [8,9] This approach enhances the consistency and reliability of the data, which is particularly important in retrospective studies. Furthermore, our study employed data from a comprehensive 2-year follow-up period, which provides useful insights into the long-term durability of treatment response and outcomes.

Our research, however, has several limitations. First, our study is limited by its retrospective nature and single-center design., limiting the generalizability of the obtained results. Second, the study did not evaluate the impact of specific neoadjuvant chemotherapy or radiotherapy regimens on the incidence of pCR, which may be relevant in clinical decision-making. Others include the single-center nature of the study and the potential for selection bias. Finally, the study did not evaluate the quality of life or functional outcomes of patients, which are important considerations in cancer treatment. The findings of this study may not be generalizable to other populations or settings.

Conclusion

The present study provides important insights into the effectiveness of TNT in the treatment of locally advanced rectal adenocarcinoma. Our findings demonstrate that TNT is provides better pCR and support the incorporation of TNT as a standard treatment approach in locally advanced rectal adenocarcinoma. Despite these limitations, our study adds to the growing body of evidence supporting the use of TNT in the treatment of locally advanced rectal adenocarcinoma. Thecurrent study provides important insights into the effectiveness of TNT in a real-world setting with a standardized definition of pCR. The findings of this study hold significant clinical implications for the management of locally advanced rectal adenocarcinoma in the Indian population. The findings of this study have the potential to improve treatment decision-making and optimize therapeutic strategies for Indian patients with locally advanced rectal adenocarcinoma undergoing TNT. Further research, including multicenter randomized controlled trials, is warranted to validate these results and optimize the sequencing and duration of neoadjuvant and adjuvant therapies in rectal adenocarcinoma management.

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