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NEOADUJAVNT SHORT COURSE RADIATION THERAPY AND CHEMOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER (SINGLE INSTITUTE STUDY)

Muhammad Ayaz[1*], Ahsan Mahmood[2], Muhammad Sohaib Nadeem[3], Khurram Khan[4], Kashif Ali Sarwar[5]

[1]*Resident Radiation Oncology, Combined Military Hospital Rawalpindi, Email: ayazafridi201217@gmail.com
[2]Professor and Head Department of Radiation Oncology, National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi, Email: ahsan_mahmood@hotmail.com
[3]Consultant Radiation Oncology, National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi, Email: sohaib63@yahoo.com
[4]Senior Medical Physicist, National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi, Email: Khurramkhan1989@ymail.com
[5]Resident Radiation Oncology, National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi, Email: Kashifsarwar11@gmail.com

***Corresponding Author:** Muhammad Ayaz
*Email: ayazafridi201217@gmail.com

Abstract:

Objectives: To evaluate the clinical and pathological response after neoadjuvant short course radiation therapy followed by chemotherapy followed by Surgery in patients suffering from locally advance rectal adenocarcinoma.

Materials and Methods: Patients with rectal and rectosigmoid adenocarcinoma at National University of Medical Sciences (NUMS) Tertiary care Hospital Rawalpindi were assessed, meeting criteria and discussed in a multi-disciplinary team. After consent, they underwent clinical examination and received 25 Gray (Gy) radiotherapy in 5 daily fractions, over one week, followed by six chemotherapy courses with Capecitabine and Oxaliplatin, then total mesorectal excision. Disease response was evaluated radiologically using RECIST criteria and histopathology reports. Data was collected via a questionnaire and analyzed with SPSS v 25.0.

Results: The mean age of all enrolled 27 patients was 53.00±8.03 years with mean tumor size of 3.92±0.87 cm. Out of total patients 17(63.0%) were male while the remaining 10(37.0%) were female. Among the patients, 2 (7.4%) were aged between 18 and 40 years, while 7 (25.9%) were between 41 and 50 years. The majority of the patients, 15 (55.6%), were in the 51 to 60 years age group. Additionally, 3 patients (11.1%) were older than 60 years. In this study, the mortality rate was 7.4%, with 2 patients having died, while 25 patients (92.6%) survived. Clinical down staging occurred in 22 patients (81.5%), while 5 patients (18.5%) did not experience down staging. The histopathological response category analysis showed that 14 patients (51.9%) had a complete response to treatment, 9 patients (33.3%) had a partial response, and 4 patients (14.8%) had no response. Stratification of response categories with respect to age groups, gender, and tumor size was done as: In terms of gender, 9 males (52.9%) achieved a complete response, 5 males (29.4%) had a partial response, and 3 males (17.6%) had no response. For females, 5 (50%) had a complete response, 4 (40%) had a partial

response, and 1 (10%) had no response, with a P-value of 0.79. Regarding age groups, for those aged 18-40 years, 2 patients (14.3%) had a complete response, with no partial response or no response cases reported. In the 41-50 years age group, 3 patients (42.85%) had a complete response, 3 patients (42.85%) had a partial response, and 1 patient (14.3%) had no response. Among those aged 51-60 years, 9 patients (60.0%) had a complete response, 5 patients (33.33%) had a partial response, and 1 patient (6.67%) had no response. For patients over 60 years, none had a complete response, 1 patient (33.33%) had a partial response, and 2 patients (66.67%) had no response, with a P-value of 0.12. In terms of tumor size, patients with tumors less than 4 cm had a higher complete response rate (10 patients, 50.0%) and a partial response rate of 9 patients (45.0%), with only 1 patient (5.0%) showing no response. For tumors larger than 4 cm, 4 patients (80.0%) had a complete response, none had a partial response, and 1 patient (20.0%) had no response, with a P-value of 0.16.

Conclusion: It was concluded that neoadjuvant therapy is a valuable approach for treating locally advanced rectal cancer with no high risk features. This regimen presents a promising strategy for managing advanced cases and offers practical insights into the implementation of these treatments within a specific institutional context.

INTRODUCTION: Locally advanced rectal cancer poses a significant challenge in oncology, necessitating comprehensive treatment approaches to enhance outcomes and minimize recurrence risks. Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide, with more than 30% originating in the rectum.(1, 2) Additionally, it is the second leading cause of cancer-related deaths.(1) The main treatment for rectal cancer is surgery. However, for patients with locally advanced disease, neoadjuvant radiation therapy (RT) is recommended to help lower the risk of local recurrence.(3) Neoadjuvant therapy, which integrates short course radiation therapy (SCRT) with chemotherapy, has become a cornerstone in improving tumor response and preparing for surgical intervention. Currently, there are three primary regimens for administering radiation in locally advanced rectal cancer (LARC): (i) short-course radiotherapy alone (SCRT; 25 Gy in 5 fractions) with either immediate surgery (within 1 week) or delayed surgery (after 4-8 weeks), and (ii) long-course chemoradiotherapy (LCRT; 45-50.4 Gy in 25-28 fractions with concurrent chemotherapy) followed by surgery after 6-8 weeks.(4) (iii) short-course radiotherapy (25 Gy in 5 fractions) followed by 6 cycles of capecitabine/Oxaliplatin then surgery (after 4-8 weeks). Typically, SCRT with immediate or delayed surgery is utilized for patients with intermediate risk factors for local recurrence and mesorectal fascia is not threatened or involved, while LCRT is preferred for patients with larger tumors or N2 nodal disease or mesorectal fascia involvement. Both approaches generally result in similar outcomes concerning surgical effectiveness, long-term oncologic results, late toxicity, and overall quality of life.(5-7).For high risk locally advanced disease including cT4, cN2, involved Mesorectal fascia, EMVI, RAPIDO trial now indicate higher locoregional recurrence rate.

Rectal cancer is increasingly prevalent in Pakistan, with many patients presenting at advanced stages due to late diagnosis. represents a promising approach for treating locally advanced rectal cancer. This study aims to evaluate the effectiveness of this regimen in reducing tumor size, improving surgical outcomes and getting higher locoregional control of cancer.

Objective:

To evaluate the clinical and pathological response after neoadjuvant short course radiation therapy followed by chemotherapy followed by surgery in patients suffering from locally advance rectal malignancy.

MATERIALS AND METHODS:

Study Design: Prospective interventional study.

Study setting: National University of Medical Sciences (NUMS) Tertiary Care Hospital at Rawalpindi (Pakistan).

Duration of the study: Duration of the study was 6 months (Nov 2022-May 2023).

Sample size: The sample size of 27 patients was calculated by using WHO sample size calculator keeping absolute precision to 10%, level of confidence to 95% and anticipated population proportion to 75%.

Inclusion Criteria:

- ECOG PS 0 and 1.
- Patients of age 18-80 years.
- Histopathologically confirmed adenocarcinoma of rectum and rectosigmoid junction
- Both male and female patients.
- Stage: Clinical cT3 or node positive (N1) disease by MRI, without breech or threatening of mesorectal fascia (MRF).
- Patients who have not taken oncological treatment for the same disease before starting short course radiation.

Exclusion Criteria:

- Patients with metastatic (M1) disease confirmed by imaging or pathologically.
- Patients having radiation precluding conditions like ulcerative colitis and pregnancy.

Methods:

All consecutive patients suffering from adenocarcinoma of the rectum and rectosigmoid junction who presented to the Radiation Oncology department of NUMS University Tertiary care hospital Rawalpindi were assessed, and those fulfilling the inclusion and exclusion criteria were selected and discussed in a multi-disciplinary team meeting. After obtaining informed consent, patients were examined clinically, including digital rectal examinations. All patients underwent a planning computed tomography (CT), which was performed on Canon (AQUILION LB 16 slice) in the supine treatment position. The ECLIPSE 16.1 version treatment planning software (Varian) was used for contouring and treatment planning. Radiation therapy was delivered through VMAT technique. All treatments were delivered using 6MV Photons from a Varian CLINAC-DHX, to a total radiation dose of 25 Gy in 5 fractions of radiotherapy over one week from Monday to Friday, followed by 6 courses of chemotherapy with Capecitabine and Oxaliplatin. Oral Capecitabine 1000 mg/m² was administered twice a day within 30 minutes of a meal for 14 days, followed by 7 days off, and oxaliplatin 130 mg/m² was given once every 3 weeks, followed by total mesorectal excision after 4-6 weeks of Neoadjuvant treatment. The clinical response of the disease was assessed radiologically with contrast enhanced Magnetic resonance imaging (MRI) pelvis and Contrast enhanced computed tomography chest and abdomen as per RECIST criteria version 1.1 after Neoadjuvant therapy, and the pathological tumor response was evaluated in the histopathology report as per tumor regression grade after surgery. A predesign questionere was used to collect the data. SPSS (Version 25.0) was used for statistical analysis.

RESULTS:

The mean age of all enrolled 27 patients was 53.00±8.03 years with mean tumor size of 3.92±0.87 cm. Out of total patients 17(63.0%) were male while the remaining 10(37.0%) were female. Among the patients, 2 (7.4%) were aged between 18 and 40 years, while 7 (25.9%) were between 41 and 50 years. The majority of the patients, 15 (55.6%), were in the 51 to 60 years age group. Additionally, 3 patients (11.1%) were older than 60 years. In this study, the mortality rate was 7.4%, with 2 patients having died after surgery, while 25 patients (92.6%) survived. Down staging occurred in 22 patients (81.5%), while 5 patients (18.5%) did not experience down staging. The response category analysis showed that 14 patients (51.9%) had a complete response to treatment, 9 patients (33.3%) had a partial response, and 4 patients (14.8%) had no response. Stratification of response categories with respect to age groups, gender, and tumor size was done as: In terms of gender, 9 males (52.9%) achieved a complete response, 5 males (29.4%) had a partial response, and 3 males (17.6%) had no response. For

females, 5 (50%) had a complete response, 4 (40%) had a partial response, and 1 (10.0%) had no response, with a P-value of 0.79.

Regarding age groups, for those aged 18-40 years, 2 patients (14.3%) had a complete response, with no partial or no response cases reported. In the 41-50 years age group, 3 patients (21.4%) had a complete response, 3 patients (33.3%) had a partial response, and 1 patient (25.0%) had no response. Among those aged 51-60 years, 9 patients (64.3%) had a complete response, 5 patients (55.6%) had a partial response, and 1 patient (25.0%) had no response. For patients over 60 years, none had a complete response, 1 patient (11.1%) had a partial response, and 2 patients (50.0%) had no response, with a P-value of 0.12. In term of tumor size, patients with tumors less than 4 cm had a higher complete response rate (10 patients, 71.4%) and a partial response rate of 9 patients (100.0%), with only 1 patient (25.0%) showing no response. For tumors larger than 4 cm, 4 patients (28.6%) had a complete response, none had a partial response, and 3 patients (75.0%) had no response, with a P-value of 0.16.

Table 1: Mean age of all enrolled Patient *(n=27)*

Variables	**Mean±SD**
Age (Years)	53.00±8.03
Tumor size (cm)	3.92±0.87

Table 2: Characteristics of all the enrolled patients *(n=27)*

Gender	Frequency	Percentage
Male	17	63.0
Female	10	37.0
Age groups		
18-40 years	2	7.4
41-50 years	7	25.9
51-60 years	15	55.6
>60 years	3	11.1
Mortality		
Yes	2	7.4
No	25	92.6
Down Staging		
Yes	22	81.5
No	5	18.5
Response category		
Complete Response	14	51.9
Partial Response	9	33.3
No Response	4	14.8

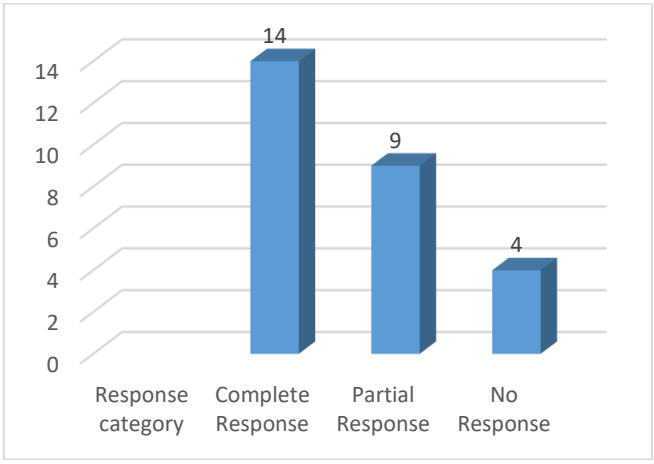

Fig 1: Frequency of response category

Table 3: Stratification of Response category with respect to age groups, gender and tumor size *(n=27)*

Age groups	Response category			P-value
	Complete response	Partial response	No response	
Gender				
Male	9(64.3%)	5(55.6%)	3 (75.0%	0.79
Female	5(35.7%)	4(44.4%)	1(25.0%)	
Age group				
18-40 years	2(14.3%)	0(0.0%)	0(0.0%)	
41-50 years	3(21.4%)	3(33.3%)	1(25.0%)	
51-60 years	9(64.3%)	5(55.6%)	1(25.0%)	0.12
>60 years	0(0.0%)	1(11.1%)	2(50.0%)	
Tumor size (cm)				
≤4	10(71.4%)	9(100.0%)	1(25.0%)	
>4	4(28.6%)	0(0.0%)	3(75.0%)	0.16

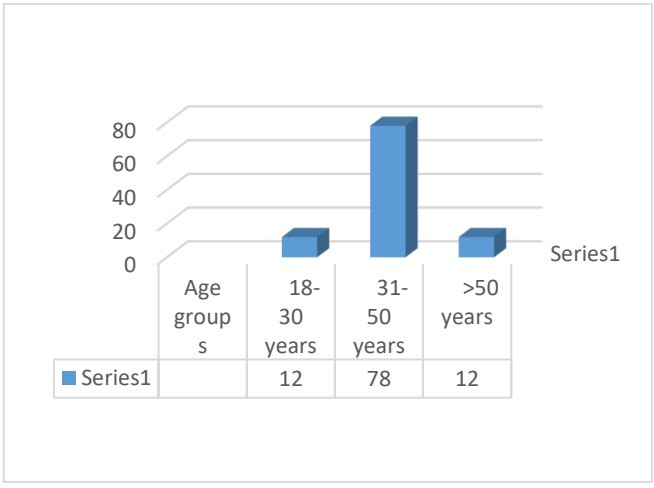

FIG 2: Patients distribution on the basis of age groups

Discussion:

The present study reported a very low mortality rate, resulting in a high overall survival rate of 92.6%. This suggests that this treatment approach has the potential to significantly improve life expectancy. Similar survival rates have been observed in other studies examining neoadjuvant therapies. In a study

conducted by Bahadoer et al.(8) found that SCRT followed by chemotherapy resulted in an overall survival rate of around 89% after three years, demonstrating the effectiveness of this regimen. The RAPIDO trial (reference) also reported a comparable survival rate of approximately 89%, further supporting the potential of neoadjuvant SCRT to reduce mortality.

Radiologically, down staging is typically assessed using MRI (9) as assessed in the present study. This tool allow for detailed visualization of the tumor and surrounding structures, enabling clinicians to evaluate the extent of the tumor before and after treatment.(10, 11) In rectal cancer, MRI is often considered the gold standard for assessing tumor response, particularly in evaluating the tumor's relationship with the mesorectal fascia, which is critical for determining resectability.(12, 13) In the present study, 81.5% of patients showed down staging after neoadjuvant short-course radiation therapy (SCRT) and chemotherapy, highlighting the regimen's success in shrinking tumors and potentially improving surgical outcomes. From a radiological perspective, such down staging would typically be seen as a decrease in tumor volume, reduced involvement of adjacent structures, and a change in the tumor's T stage (e.g., from T3 to T2/1/0), all of which would be evident on follow-up imaging.

The present study finding is consistent with the results from other studies on neoadjuvant chemoradiotherapy for locally advanced rectal cancer, where downstaging rates typically range from 70% to 80%. The German Rectal Cancer Study Group reported a downstaging rate of approximately 70% in patients receiving preoperative chemoradiotherapy, which was associated with a higher rate of sphincter preservation and lower recurrence rates.(14) The RAPIDO trial (15), which also investigated the use of SCRT followed by chemotherapy, reported a significant impact on down staging, with a high percentage of patients achieving tumor reduction before surgery. This further supports the notion that SCRT, when paired with chemotherapy, is an effective neoadjuvant strategy for optimizing surgical and long-term outcomes in patients with locally advanced rectal cancer.

The stratifications of the present study provide a detailed view of how different factors might influence treatment outcomes, though the p-values suggest that these differences may not reach statistical significance.

This study on the combination of neoadjuvant short-course radiation therapy (SCRT) and chemotherapy in locally advanced rectal cancer offers valuable insights into the effectiveness and potential outcomes of this treatment regimen. With the global incidence of rectal cancer on the rise, it is increasingly important to refine treatment strategies that enhance patient outcomes while reducing treatment-related morbidity. This study conducted at a single institute highlights the practicality and success of using SCRT followed by chemotherapy as a neoadjuvant strategy. Short-course radiation therapy, which involves administering a higher dose of radiation in a shorter timeframe, is designed to shrink the tumor and increase the chances of successful surgical removal. Following this, chemotherapy is administered to target micrometastases and boost the overall effectiveness of the treatment.

Conclusion: It was concluded that the use of neoadjuvant therapy is a valuable approach in the treatment of locally advanced rectal cancer. This regimen not only offers a promising strategy for managing advanced cases but also provides insights into the practical application of these treatments within a single institutional setting.

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