ORIGINAL ARTICLE

Assessment of Response to Concomitant Chemoradiation with Capecitabine in Locally Advanced Rectal Carcinoma: A Descriptive Observational Study from Nishtar Hospital, Multan

Ferwa Nasir[1*], Aalia Bashir[2], Muhammad Junaid Hassan[3], Tariq Jamil[4]

ABSTRACT

Objective: To assess the response of preoperative concomitant chemo-radiation with capecitabine in patients with locally advanced rectal carcinoma.

Study Design: A descriptive observational study.

Place and Duration of Study: This study was conducted at the Department of Oncology, Nishtar Hospital, Multan, Pakistan from 5th November 2024 to 5th May 2025.

Methods: A total of 100 patients aged 18-70 years old, diagnosed with stage 3 or 4 non-metastatic rectal adenocarcinoma, were included. Protracted radiotherapy at 50.4 Gray was delivered over 5.5 weeks, with 1.8 Gray per session, five days a week. An 825 mg/m2 dose of Capecitabine was administered orally twice a day through the radiotherapy course, including weekends, along with the start of radiotherapy. Surgery was performed 4-6 weeks after the concurrent treatment and the technique was chosen according to the surgeon's discretion. Adjuvant chemotherapy of four cycles of IV 5-FU (400 mg/m2) and leucovorin (20 mg/ m2) was started four to six weeks postoperatively.

Results: Frequent grade I and II toxicity included anemia (70%), abdominal pain (50%), proctitis (42%), and nausea (46%). Capecitabine treatment was stopped in 25 patients due to grade III and IV diarrhea (37%), abdominal pain (14%), and proctitis (33%), but it did not have a significant impact on compliance. The radiotherapy compliance was 90% and 93% capecitabine dose was administered as the total dose. A pathologic complete response was reached in 8 patients (8%). Tumor downstaging was achieved in 55% of patients, and nodal down staging was observed in 50% of patients.

Conclusion: Concurrent chemoradiotherapy with capecitabine is a safe and well-tolerated treatment in patients with locally advanced rectal cancer. It has comparable efficacy to 5-FU chemotherapy and can be used as an alternative to achieve similar outcomes.

Keywords: *Capecitabine, Carcinoma, Chemotherapy, Radiotherapy, Rectal Cancer.*

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[1]*Department of Oncology/Radiotherapy/Surgery*[4]
Bakhtawar Amin Memorial Trust Hospital, Multan, Pakistan
[2]*Department of Radiotherapy/Oncology*
Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan
[3]*Department of Clinical Oncology/Radiotherapy*
Nishtar Hospital, Multan, Pakistan

Correspondence:
Dr. Ferwa Nasir
Department of Oncology/Radiotherapy
Bakhtawar Amin Memorial Trust Hospital, Multan, Pakistan
E-mail: drm95435@gmail.com

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Introduction

Rectal cancer is among the top ten common cancers in Pakistan and the leading cause of death among patients.[1] It comprises 20–30% of all cancers, while symptoms associated with it include hematochezia, tenesmus, and rectal mass. The most common type (95%) of rectal tumors is adenocarcinomas. In contrast to the West, the incidence is low in the Asian population.[2] The geographical variation in the incidence of rectal cancer is attributed to both genetic and environmental factors.

With advancements in the medical field in the modern era, the management of locally advanced rectal cancer has evolved with time. Surgery is the cornerstone for its management and cure, but when used alone, the incidence of local failure is high. This led to the improvement of new treatment options for better local control and survival. Total Mesorectal Excision (TME) is now the standard approach in rectal surgery for better local control.

Recent studies have investigated chemo-radiation either pre or post-operatively in an attempt to improve local control and survival. A multivariate analysis of another study showed that pre-operative chemoradiation therapy resulted in tumor downstaging in 62% of patients, compared with 42% in pre-operative radiotherapy alone.[3] In a general Tertiary Care Hospital setting in Pakistan, state-of-the-art facilities for ERT delivery and expertise for optimal radical surgery are lacking. This reduces the chances of a possible cure or long-term survival even in early-stage disease.

Capecitabine is an oral fluoropyrimidine that is converted to 5-FU by the enzyme Thymidine Phosphorylase (TP) at the tumor site, where there is higher TP activity than in healthy tissue. It showed a better response rate and safety profile than 5-FU/leucovorin for metastatic colorectal cancer.[4,5] Various doses of capecitabine have been used in different studies; the recommended dose is 825 mg/m^2 twice daily throughout the radiation period without any break.[6] However, the current standard treatment of locally advanced rectal carcinoma is concomitant chemo-radiation using continuous infusion of 5-FU as a radiosensitizer.[7] Several attempts have been made to improve its efficacy by combining it with leucovorin or using it as a bolus or continuous infusion, so if an agent with less toxicity is used, the response rate may further be improved, resulting in better tumor control. It is an oral alternative that may lead to high patient compliance.

There is scant data to assess the efficacy of concomitant chemo-radiation using capecitabine in locally advanced rectal cancer. The objective of the present study is to determine the response of preoperative concomitant chemo-radiation with capecitabine in patients with locally advanced rectal carcinoma. If it is found to be high, the same may be used to treat such cases. If this regimen is found to be as effective as the conventional regimen, it will definitely benefit the patients as a more convenient, oral alternative to prolonged intravenous infusions of 5-FU and simplify chemo-radiation.

Methods

A descriptive observational study was conducted at the Oncology Department of Nishtar Hospital, Multan, over 6 months from 5th November 2024 to 5th May 2025. A total of 100 patients aged 18-70 years old, diagnosed with stage 3 or 4 non-metastatic rectal adenocarcinoma within 15 cm of the anal verge through histology or positive node involvement on imaging, ECOG score ≥2, and intact liver and kidney function and bone marrow reserve were included in the study by non-probability consecutive sampling. The ECOG score is a performance scale used to evaluate the ability of patients to perform daily activities from 0 to 5, with a higher score indicating greater disability. The sample size was calculated among a population size of 135 patients, keeping a 95% confidence interval, 5% error margin, and 50% population proportion. Patients who had received chemotherapy or radiation before, had metastatic rectal cancer, had any chronic illness, had a history of carcinoma except early-stage cervical cancer or non-melanoma skin cancer, or were pregnant were excluded. The Institutional Ethical Review Board of Nishtar Hospital has approved the study vide letter no: 18945/NMU, dated: 2nd November 2024 and all patients were enrolled after giving informed consent.

All patients were physically examined, and their medical history was recorded before the start of treatment. They were evaluated for surgery before enrollment, including measurement of the distance between tumor and anal verge, the condition of the rectal cavity, adhesion to the pelvic wall, tumor laterality, and selection of surgical approach between anterior or abdominoperineal resection. Additionally, laboratory parameters including blood count, liver and kidney functionality tests, carcinoembryonic antigen, and radiological tests including abdominal CT, chest X-ray, endoscopic ultrasound, and colonoscopy were performed (Figure. 1).

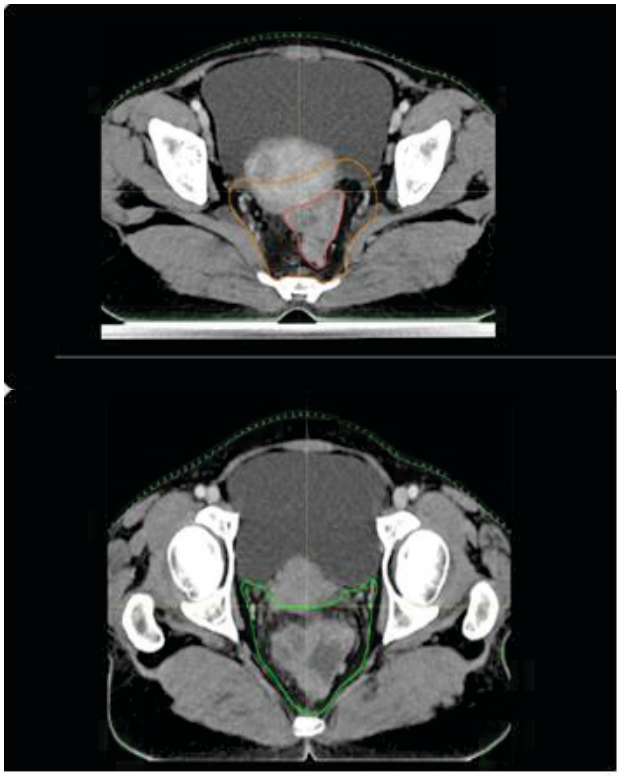

Fig.1: Images showing Radiation planning on CT-Sim for locally advanced rectal carcinoma

The treatment plan involved concomitant administration of capecitabine along with radiotherapy before surgical resection. Protracted radiotherapy treatment of 50.4 Gray was delivered over 5.5 weeks, with 1.8 Gray per session, five days a week. Patients were positioned in a prone position by a three-dimensional simulator. A 3- or 4 4-field treatment technique targeted the main tumor area and surrounding lymph nodes in the presacral and internal iliac region. The linear accelerator delivered 10 MV energy for front and back beams and 18 MV for side beams, and initially delivered 45 Gray in 25 sessions on a larger area for 5 weeks. A boost dose of 5.4 Gray was given in 3 sessions to just the tumour area, keeping a 2 cm safety margin. The radiation dose was carefully aimed and calculated to hit the middle of the tumor accurately, following the ICRU report 50/62 guidelines, which define target volumes and standardized dose prescription in radiotherapy.

Chemotherapy was started concurrently with the radiotherapy. An 825 mg/m^2 dose of Capecitabine was administered orally twice a day through the radiotherapy course including at weekends. The dose was interrupted for patients with grades 3 or 4 diarrhea or hand-foot syndrome unless the conditions improved or resolved and then continued at 75% of the original dose or a reduced dose.

Surgery was performed 4-6 weeks after concurrent treatment, and the technique was selected at the surgeon's discretion. Adjuvant chemotherapy of four cycles of IV 5-FU (400 mg/m^2) and leucovorin (20 mg/m^2) was started four to six weeks postoperatively. The cycles were administered every 4 weeks for 5 days a week. Emesis was prevented by prescribing antiemetics. The dose was modified by 20% in patients experiencing diarrhea, febrile neutropenia, or grade III stomatitis. If toxicity exceeded grade 3 or higher, therapy was stopped. All laboratory and radiological tests were repeated 8 weeks after the last chemotherapy session.

After completion of total mesorectal excision, the specimen was visually inspected and graded according to the Quirke grading system.[8] The Quirke grading system assesses the quality of mesorectal excision by examining its integrity as complete, nearly complete, or incomplete. The excision was complete if the mesorectum was smooth and intact. Any cut, tear, or damage in the tissue should not be more than 5 mm, the specimen should have uniform thickness and no tapering, and the outer edge should be even and smooth. Surgical margins were evaluated, and mesorectal fat was marked along with the bare front and back areas. The rectum was opened from the front, excluding the 4 cm around the tumor. The size and depth of tumor were noted. The specimen was then stretched out and preserved in fixative for at least 48 hours. After that, the unopened tumor area was cut into 3-5 mm thin slices to further assess the quality of excision, tumor depth, and how close it was to the outer inked, which is key in predicting chances of cancer coming back locally. Three of these samples were labelled and sent for microscopic analysis. If the tumor was near the margin, the shortest distance was recorded. To examine the lymph nodes, the surrounding fat was cut into 1mm sections and sent for histology.

All data was analyzed by SPSS version 20. Patients' characteristics and treatment complications were presented as frequencies and percentages.

Results

The median age of patients was 52 years, with the majority of male patients (60%). A total of 79 (79%) patients had an ECOG score of 1. 68 (68%) patients had a tumor of 5 cm or smaller. The median distance between tumor and anal verge was 5 cm for the study population and 2.5 cm for patients who underwent abdominoperineal resection. 68 (68%) had a stage 3 tumor, 20 (20%) had a stage 4 tumor, and 59% tumors had node involvement. The characteristics of patients are shown in Table 1.

Table 2 shows the toxicities of concomitant radiotherapy and capecitabine treatment, indicating that it was generally safe and well tolerated. None of the complications caused deaths. Frequent grade I and II toxicity included anemia (70%), diarrhea (26%), abdominal pain (50%), hand and foot syndrome (27%), proctitis (42%), leukopenia (46%), nausea (46%) and vomiting (20%), anorexia (40%) and dysuria (40%). Capecitabine treatment was stopped in 25 patients due to grade III and IV diarrhea (37%), abdominal pain (14%), and proctitis (33%), but it did not have a significant impact on compliance. The radiotherapy compliance was 90% and 93% capecitabine dose was administered as the total dose.

Table 1: Patients Demographic and Tumor Characteristics

Characteristics	N (%)
Median age	52 (25-70)
Gender	
Male	60 (60%)
Female	40 (40%)
ECOG status	
0	5 (5%)
1	79 (79%)
2	16 (16%)
Distance of tumor from anal verge	
≤ 5	68 (68%)
>5	32 (32%)
Tumor staging	
T_x	5 (5%)
T3	68 (68%)
T4	20 (20%)
N-ve	35 (35%)
N+ve	59 (59%)

A pathologic complete response was reached in 8 patients (8%). The lymph node yield had a median value of 6.5 (range 0-20). The tumor staging of patients who underwent surgery is shown in Table 3. Tumor downstaging was achieved in 55% of patients, and nodal downstaging was observed in 50% of patients. Tumor and nodal downstaging were assessed by comparing pretreatment tumor grading to post-treatment pathological staging. Sixty patients (60%) did not show any evidence of node positivity.

A total of 55 patients (55%) underwent abdominoperineal resection, and 45 patients (45%) underwent sphincter-preserving anterior resection. All surgeries ended up in complete resection with clear margins, with a 42% sphincter preservation rate in patients who underwent anterior resection and 15% in patients who underwent abdominoperineal resection. All patients completed adjuvant chemotherapy.

Table 2: Adverse Effects of Concomitant Treatment

Adverse effects	Stage I and II	Stage III and IV
Leukopenia	46 (46%)	5 (5%)
Anemia	70 (70%)	5 (5%)
Thrombocytopenia	5 (5%)	5 (5%)
Granulocytopenia	20 (20%)	5 (5%)
Hand and foot syndrome	27 (27%)	-
Nausea	46 (46%)	5 (5%)
Vomiting	20 (20%)	-
Mucositis	8 (8%)	-
Diarrhea	26 (26%)	37 (37%)
Proctitis	42 (42%)	33 (33%)
Abdominal pain	50 (50%)	14 (14%)
Hypokalemia	-	10 (10%)
Hypocalcemia	-	5 (5%)
Hypomagnesemia	-	5 (5%)
Anorexia	40 (40%)	5 (5%)
Hypotension	5 (5%)	7 (7%)
Hyperbilirubinemia	10 (10%)	-
Hyponatremia	10 (10%)	7 (7%)
Fatigue	26 (26%)	7 (7%)
Constipation	10 (10%)	-
Chest pain	-	5 (5%)
Dizziness	14 (14%)	5 (5%)
Dehydration	-	7 (7%)
Fever	7 (7%)	-
Urinary tract infection	5 (5%)	-
Dysuria	40 (40%)	-

Table 3: Outcomes of Tumor Staging After Treatment

	pT0	pT1	pT2	pT3	pT4
uT3	7 (7%)	-	25 (25%)	34 (34%)	5 (5%)
uT4	-	-	5 (5%)	10 (10%)	5 (5%)

Discussion

This study was conducted to evaluate the outcome of preoperative concomitant treatment of 50.4 Gray radiotherapy and 825 mg capecitabine in patients with locally advanced rectal cancer. The results showed that the treatment was safe and well-tolerated. The grade I and II toxicities reported in our study were comparable to the literature, with a 20-40% frequency of diarrhea and a 20-25% incidence of hand and foot syndrome.[9,10] The most common severe complications were proctitis (33%) and diarrhea (37%), which is higher than the previous studies. Hills R et al. reported the frequency of grade III and IV diarrhea in 13% of patients, Bisht N et al. in 7% of patients, and Mashhour K et al. in 5% of patients.[11-13] The significant difference can be due to patients' characteristics such as diet and race. However, this level of toxicity did not significantly affect treatment compliance, as it occurred near the end of concurrent treatment, and it moderately affected radiation compliance and capecitabine dosage.

After the treatment, tumor downstaging was observed in 55% of patients, with node reduction in 50% of patients. Some authors agree with our tumor staging, while others report downstaging in 75-85% of patients.[14-16] A complete response was only achieved by eight patients (8%), with 20% of these having a stage 4 tumor. There is a significant discrepancy in complete response rates in a study conducted on concurrent capecitabine therapy. Puri R et al. conducted a study on a similar pattern as our

study and reported a pathologic complete response (pCR) rate, which is the absence of any residual viable tumor cells in the resected specimen after chemoradiotherapy, of 30% among which 90% of patients had a stage 3 tumor.[17] Similarly, Huang CW et al. reported a complete response in 5% of patients, but half of the patients in the study had stage 4 carcinoma.[18]

68% of patients in our study had a tumor 5 cm or less from the anal verge. Still, the sphincter was preserved in only 42% of patients in anterior resection patients and 15% of abdominoperineal resection patients. This indicates that the preoperative treatment does not guarantee the preservation of the sphincter. Previous studies reported preservation rates of 60-75%, which may be explained by adopting a trans-anal full-thickness local excision approach rather than abdominoperineal excision.[19,20]

In contrast to capecitabine chemotherapy, studies conducted on 5-FU and leucovorin have reported more consistent results. Torky R et al. showed a 9% complete response rate with sphincter preservation in 40% of patients.[21] Another study reported a 6% response rate in patients who underwent chemoradiotherapy before surgery, with no difference in sphincter excision in comparison with patients who only underwent preoperative radiotherapy.[22] Similarly, a higher response rate of 12% and 16% was reported by an Indian and US study, respectively, with the same results for sphincter preservation, but a lower 5-year and 4-year overall survival rate (67.4% vs 67.2%) was observed.[23,24]

Our study has limitations. We only conducted a 1-year study, so long-term survival and recurrence could not be recorded. Additionally, we excluded patients with evidence of metastasis so outcomes of concurrent therapy could not be assessed in critical cases. However, we recommend larger local studies to evaluate long-term outcomes with our treatment regimen. Also, more studies must be conducted with other novel agents, including cetuximab, which has shown promising results in trials of metastatic rectal carcinoma. Concurrent radiotherapy is reported to improve survival in other types of local carcinomas.

Conclusion

Concurrent chemoradiotherapy with capecitabine is a safe and well-tolerated treatment in patients with locally advanced rectal cancer. It has comparable efficacy to 5-FU chemotherapy and can be used as an alternative to achieve similar outcomes. Since the response rate is high, this treatment can be used for rectal cancer patients.

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Conflict of Interest: The authors declare no conflict of interest

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Author Contributions

FN: Conception and design of the work, manuscript writing for methodology design and investigation, writing the original draft, proofreading, and approval for final submission

AB: Data acquisition, curation, and statistical analysis

MJH: Validation of data, interpretation, and write-up of results

TJ: Revising, editing, and supervising for intellectual content