Published Online: 2025 February 26 **Research Article**

Investigating Predictive Factors of Pathological Complete Response After Neoadjuvant Chemoradiotherapy in Patients with Locally Advanced Rectal Cancer

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Received: 8 January, 2025; **Accepted:** 15 January, 2025

Abstract

Background: Standard treatment for locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiotherapy (CRT) followed by surgery and adjuvant chemotherapy. Although achieving a pathological complete response (pCR) is considered a favorable prognostic factor, the parameters influencing pCR remain incompletely defined.

Objectives: This study investigated predictive factors for achieving pCR in patients with LARC who underwent neoadjuvant CRT.

Methods: This retrospective cross-sectional study included 100 patients with LARC who underwent neoadjuvant CRT between May 2018 and September 2023 at Shohadaye Tajrish Hospital, Tehran, Iran. Patients' demographics, clinicopathological data, and treatment details, including chemotherapy and radiotherapy data, were reviewed to analyze their correlation with pCR. Statistical analysis was performed using the chi-square test, Student's *t*-test, and Fisher's exact test to assess factors associated with pCR. A P-value of < 0.05 was considered statistically significant.

Results: Pathological complete response was obtained in 28% of the cases. Clinical stage and induction chemotherapy were independent predictors of pCR ($P < 0.05$). Patients with T3N1 and T3N2 stages had higher pCR rates, whereas none of the T4N2 patients achieved pCR. The number of induction chemotherapy cycles was strongly associated with pCR. The pCR rates were significantly higher for those patients who received four cycles or more ($P < 0.05$). No significant association was found between pCR and age, gender, Body Mass Index (BMI), tumor differentiation, or radiotherapy dosimetry.

Conclusions: The clinical stage at diagnosis and the extent of induction chemotherapy were significant predictors of pCR in this study. Further prospective studies are warranted to validate these findings and explore additional predictive factors.

Keywords: Pathological Complete Response, Predictive Factors, Neoadjuvant Chemoradiotherapy, Locally Advanced Rectal Cancer

1. Background

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide, with an estimated 1.9 million new cases in 2022 (1). It is the third most common cancer among Iranian men, with a standardized incidence of 8.1 - 8.3 per 100,000, and the fourth most common cancer in women, with a standardized incidence of 6.5 to 7.5 per 100,000 (2). Colorectal cancer is the second most prevalent cause of cancer-related death worldwide (3). Currently, the standard treatment for patients with locally advanced rectal cancer (LARC) consists of neoadjuvant chemoradiotherapy (CRT), followed by surgical resection and adjuvant chemotherapy (4). This multimodal approach aims to reduce tumor size and stage, facilitating surgical resection and improving outcomes such as sphincter preservation and local recurrence (5, 6).

Different pathological and clinical features carry prognostic significance in CRC, such as tumor-node-metastasis (TNM) staging, histological grade, resection margin status, perineural invasion (PNI), lymphovascular invasion (LVI), and pre-treatment carcinoembryonic antigen (CEA) (7, 8). Recently, the pathological response to neoadjuvant treatment has garnered significant attention as an important prognostic factor. It has been suggested that pathological complete response (pCR), defined as the absence of viable tumor cells in resected specimens — is a crucial determinant of prognosis and is significantly associated with lower recurrence rates and improved survival (9). Approximately 10% - 30% of patients achieve pCR, with no viable tumor cells in their surgical specimens (10). These patients show superior overall and disease-free survival compared to non-pCR patients, highlighting the potential benefits of predicting a patient's response to neoadjuvant CRT (11). In one study, the 5-year recurrence-free survival rates were 90.5%, 78.7%, and 58.5% for patients with complete, intermediate, and poor responses, respectively (12). Since patients who achieve pCR have a better prognosis, it is proposed that their treatment strategy may differ from those without pCR. However, the factors that predict patient response to neoadjuvant CRT for rectal cancer remain poorly defined.

2. Objectives

To our knowledge, there is limited data on factors predicting patient response to neoadjuvant CRT for rectal cancer in Iran. Given the high prevalence of rectal cancer and the critical importance of achieving pCR, this study aimed to investigate predictive factors for pCR in patients with LARC who underwent neoadjuvant therapy at Shohadaye Tajrish Hospital in Tehran, Iran.

3. Methods

This retrospective cross-sectional study was conducted on patients diagnosed with LARC who underwent neoadjuvant CRT at Shohadaye Tajrish Hospital in Tehran, Iran, between May 2018 and September 2023.

Patients with biopsy-confirmed adenocarcinoma of the rectum who had undergone neoadjuvant CRT with or without induction chemotherapy followed by radical resection were included. Patients were excluded if they had recurrent or metastatic disease, a history of chemotherapy or pelvic radiotherapy, or had undergone local excision. After obtaining Institutional Review Board approval (IR.SBMU.MSP.REC.1400.201), the medical records of eligible patients were reviewed.

All patients underwent preoperative staging with pelvic magnetic resonance imaging (MRI) and computed tomography scans (CT) of the abdomen and chest. The tumor location was determined according to the distance from the anal verge during colonoscopy. Tumors located more than 10 - 15 cm from the anal verge were classified as upper rectal tumors, while those within 5 cm of the anal verge were categorized as lower tumors. Tumors located between 5 and 10 cm from the anal verge were considered mid-tumors. Lymph node metastasis was evaluated using pelvic MRI to assess the size, irregular margins, and heterogeneous signal intensity. Tumor size was determined based on the longitudinal tumor measurement on MRI.

The above results were officially reported by a radiologist specializing in CRC. The stage was determined according to the eighth edition of the American Joint Committee on Cancer Staging (AJCC, 2017). Patients with clinical T3 or higher or clinical nodal involvement were determined as LARC and received neoadjuvant CRT. All patients received at least six months of neoadjuvant or adjuvant chemotherapy. The chemoradiation regimen consisted of long-course radiation (4500 to 5040 cGy) over 5 - 6 weeks with concurrent oral capecitabine (825 mg/m^2 twice a day on the days of radiation). Three-dimensional conformal radiation therapy (3D-CRT) with 6 MV photons was applied by a linear accelerator (LINAC) (Varian Medical Systems Inc., Palo Alto, CA). Contouring was performed on planning CT scan with 5 mm slice thickness, considering each patient's MRI images that fused with CT scan and colonoscopy findings. The patients' radiotherapy plans were reviewed for dosimetric parameters. Surgery was performed 6 to 8 weeks after completion of chemoradiation. All chemotherapy regimens used the modified FOLFOX6 regimen. The pCR was defined as the absence of viable cancer cells observed in the specimen after radical resection. Demographic data, including age, gender, Body Mass Index (BMI), TNM stage, and radiation treatment data were collected using a standardized checklist (Table 1).

3.1. Statistical Analysis

Statistical analyses were performed using SPSS software, version 26. The Shapiro-Wilk test was used to assess the normality of the distribution of quantitative data. Descriptive statistics for normally distributed data included the mean and standard deviation, whereas the median and interquartile range are used for non-normally distributed data. Qualitative data were

Table 1. Demographic and Clinical Characteristics of Patients and Their Association with Pathological Response [a]

Characteristic	Total	Complete Response	Partial Response	No Response	P-Value
Gender					0.677
Male	72	21 (29.2)	39 (54.2)	12 (16.7)	
Female	28	7 (25.0)	21 (75.0)	0 (0.0)	
Clinical stage					0.011
T3N0	14	0 (0.0)	14 (100.0)	0 (0.0)	
T3N1	61	21 (34.4)	34 (55.7)	6 (9.8)	
T3N2	19	7 (36.8)	6 (31.6)	6 (31.6)	
T4N2	6	0 (0.0)	6 (100.0)	0 (0.0)	
Tumor differentiation					0.407
Well differentiated	69	21 (30.4)	42 (60.9)	6 (8.7)	
Moderately differentiated	25	7 (28.0)	18 (72.0)	0 (0.0)	
Poorly differentiated	6	0 (0.0)	0 (0.0)	6 (100.0)	
Induction chemotherapy					< 0.001
None	53	0 (0.0)	41 (77.4)	12 (22.6)	
FOLFOX 2 cycles	6	0 (0.0)	6 (100.0)	0 (0.0)	
FOLFOX 3 cycles	7	0 (0.0)	7 (100.0)	0 (0.0)	
FOLFOX 4 cycles	27	21 (77.8)	6 (22.2)	0 (0.0)	
FOLFOX 6 cycles	7	7 (100.0)	0 (0.0)	0 (0.0)	

[a] Values are expressed as No. (%).

expressed as frequencies and percentages and summarized in descriptive tables and frequency charts. Descriptive statistical methods (mean, standard error, and median) were used. Data were analyzed using the chi-square test, Student's *t*-test, Pearson correlation, and Fisher-Freeman-Halton test. All tests were considered statistically significant when the P-value was < 0.05.

4. Results

Between May 2018 and September 2023, 130 patients with LARC who were eligible for neoadjuvant CRT were referred to our hospital. After excluding 23 patients with metastatic disease and seven who declined follow-up after CRT, the final study sample consisted of 100 patients with LARC. The mean age of the patients was 48.55 ± 15.5 years. The mean age for those who achieved pCR was 47.7 ± 10.6 years, and for those who did not, it was 48.8 ± 16.5 years, indicating no significant association between age and pCR ($P > 0.05$). There were 72 (72%) males and 28 (28%) females. Among the males, 29.2% achieved pCR, compared to 25.0% of females, indicating no significant association between gender and pCR ($P > 0.05$). The mean BMI of patients was 24.8 ± 2.9 kg/m². The mean BMI for those achieving pCR was 24.6 ± 2.5 kg/m²; for those who did not, it was 24.9 ± 3.0 kg/m², showing no significant association between BMI and pCR ($P > 0.05$) (Table 2).

Regarding clinical tumor stage, 14% of patients were classified as T3N0, 61% at T3N1, 19% at T3N2, and 6% at T4N2. None of the T3N0 patients achieved pCR, and all experienced a partial response. Among T3N1 patients, 34.4% achieved a complete response, compared to 36.8% of T3N2 patients and none of the T4N2 patients. Statistical analysis demonstrated a significant decrease in treatment response (complete and partial response) with increasing clinical stage ($P < 0.05$).

For tumor differentiation, 69% were well differentiated, 25% were moderately differentiated, and 6% were poorly differentiated. Complete response was observed in 30.4% of well-differentiated, 28% moderately differentiated, and none of the poorly differentiated tumors. Although a decrease in response was noted with poorer differentiation, this difference was not statistically significant ($P > 0.05$). Pathological complete response was achieved in 35% of patients with lower rectum tumors, 25.9% with middle rectum tumors, and 0% with upper rectum tumors. This difference was not statistically significant ($P > 0.05$).

Regarding induction chemotherapy, 53% of patients did not receive it, while 6%, 7%, 27%, and 7% received 2, 3, 4, and 6 cycles of m-FOLFOX 6, respectively. The pCR was observed only in patients who received 4 and 6 cycles, with 77.8% and 100% achieving a complete response, respectively. This significant association indicates

Table 2. Quantitative and Radiotherapy Parameters of Patients and Their Association with Pathological Response [a]

Parameters	Total	Complete Response	Partial Response	No Response	P-Value
Age (y)	48.55 ± 15.05	47.75 ± 10.64	50.73 ± 17.38	39.50 ± 4.70	0.99
BMI (kg/m²)	24.85 ± 2.92	24.65 ± 2.53	24.78 ± 3.18	25.70 ± 2.40	0.686
Interval between CRT and surgery (wk)	7.69 ± 1.36	7.25 ± 1.32	8.23 ± 1.16	6.00 ± 0.00	0.051
D95 PTV (Gy)	50.15 ± 1.83	50.33 ± 0.38	50.32 ± 2.02	48.95 ± 2.04	0.699
D100 CTV (Gy)	48.07 ± 2.57	48.30 ± 1.65	48.54 ± 2.81	45.15 ± 0.16	0.268
D100 GTV (Gy)	49.92 ± 1.87	49.70 ± 1.46	50.05 ± 1.98	49.80 ± 2.19	0.235

Abbreviations: CRT, chemoradiotherapy; BMI, Body Mass Index.

[a] Values are expressed as mean ± SD.

higher complete response rates with more induction chemotherapy cycles ($P < 0.05$).

The mean time interval between CRT and surgery was 7.6 ± 1.3 weeks. The mean interval for patients who achieved pCR was 7.2 ± 1.3 weeks, compared to 7.8 ± 1.3 weeks for those who did not achieve pCR, indicating no significant association ($P > 0.05$). Table 1 shows patients' demographic and clinical characteristics and their association with pathological response.

The mean dose of D95 PTV (the lowest dose received by at least 95% of the planning target volume) was 50.1 ± 1.8 Gy. For complete responders, the mean dose was 50.3 ± 0.3 Gy, while for non-responders, it was 50.0 ± 2.0 Gy, showing no significant difference ($P > 0.05$). The mean dose of D100 CTV (dose received by 100% of the Clinical Target Volume) was 48.0 ± 2.5 Gy, with complete responders receiving 48.3 ± 1.6 Gy and non-responders 47.9 ± 2.8 Gy, indicating no significant difference ($P > 0.05$). The mean D100 GTV (dose received by 100% of the Gross Tumor Volume) was 49.2 ± 1.8 Gy. Complete responders had a mean dose of 49.7 ± 1.4 Gy, compared to 50.0 ± 2.0 Gy for non-responders, showing no significant difference ($P > 0.05$). Table 2 demonstrates patients' quantitative and radiotherapy parameters and their association with pathological response.

5. Discussion

This study examined the clinical factors that can predict tumor response in patients with LARC who received neoadjuvant CRT at a single tertiary cancer center in Iran. We found that the clinical stage at diagnosis and the use of induction chemotherapy were significant predictors for achieving a pCR. Specifically, patients with stage T3N1 or T3N2 had higher pCR rates than those with stage T4N2. This finding aligns with previous studies that have shown that advanced tumor stages are associated with poorer response to neoadjuvant CRT (13, 14). A study by Garland et al. demonstrated that patients with lower clinical nodal stage (N1) had higher pCR rates than those with more advanced nodal involvement (N2) (15). In addition, a study by Goffredo et al. found that a lower nodal stage at diagnosis was linked to higher pCR rates (16). These findings highlight the importance of the initial tumor stage, which may help inform decisions regarding treatment for LARC patients in future cases.

The current study found a strong association between the number of induction chemotherapy cycles and the probability of achieving pCR. Patients receiving four or more cycles of m-FOLFOX 6 exhibited significantly higher complete response rates; supporting that more intensive neoadjuvant chemotherapy regimens can enhance tumor downstaging. This finding is consistent with current literature advising total neoadjuvant treatment (TNT) for LARC (17, 18). A significant study examining TNT's efficacy in LARC is the RAPIDO trial that compared the outcomes of TNT versus standard CRT followed by surgery and adjuvant chemotherapy in patients with high-risk LARC (19). In this trial, the TNT group demonstrated a significant improvement in pCR rates, with a higher rate of 28% compared to 14.3% in the standard treatment arm.

Furthermore, the TNT group exhibited a lower risk of disease-related treatment failure at 23.7% compared to 30.4% in the standard treatment arm. In a study conducted by Garcia-Aguliar et al., patients with clinical stage II–III rectal cancer were compared. The standard treatment involved long-course CRT (50.4 Gy in 28 fractions with concurrent 5-fluorouracil) followed by surgery within 6 - 8 weeks. The study also included three additional treatment arms, each involving two, four, and six cycles of consolidation FOLFOX after CRT before surgery. The pCR was increased by each additional consolidation course FOLFOX to 18%, 25%, 30%, and 38%, respectively ($P = 0.0036$) (20). The STELLAR study examined the impact of different chemotherapy

regimens and cycles on pCR rates in rectal cancer. Patients receiving extended cycles of induction chemotherapy (up to six cycles) before CRT showed improved PCR rates compared to those receiving fewer cycles (21). These findings were aligned with our results, which indicated that this approach significantly increased the pCR rates compared to standard CRT, highlighting the benefit of multiple induction chemotherapy cycles in achieving better outcomes.

The correlation between tumor differentiation and pCR in patients with LARC, has been examined in several studies; however, findings are inconsistent regarding this issue (22-25). A study by Zhong et al. found a significant correlation between tumor differentiation and the probability of pCR, reporting that well-differentiated tumors exhibited higher pCR rates than moderately and poorly differentiated tumors (23). Our present study found no correlation between tumor differentiation and pCR. These results suggest that tumor differentiation may be an important factor; however, it does not consistently predict pCR across all studies and patient populations.

Several studies have investigated the correlation between age, gender and response to neoadjuvant therapies (26, 27). The majority of these studies have consistently concluded that neither age nor gender significantly impacts the likelihood of achieving pCR (27, 28). Our study similarly found that age and gender were not significantly associated with pCR.

The BMI has been studied as a potential factor influencing the response to neoadjuvant treatment in patients with LARC (29). The impact of BMI on achieving a pCR varies across studies, with some suggesting a relationship while others do not find significant associations (29-31). In our cohort, BMI was not significantly associated with pCR in our cohort. These findings are consistent with several studies indicating that these factors do not substantially influence the efficacy of neoadjuvant CRT (32). This data indicates that BMI alone may not be a reliable predictor of treatment response and should be considered alongside other factors in managing and predicting outcomes for LARC patients. However, extreme BMI values might affect outcomes due to potential complications or altered pharmacokinetics of chemotherapeutic agents, an area warranting further investigation (29).

The interval between completing neoadjuvant CRT and undergoing surgical intervention is a critical factor influencing pCR rates in patients with LARC. The optimal time between the completion of neoadjuvant CRT and surgery in these patients is controversial (33). A study by SA Amin investigated radiotherapy to surgery intervals of 5 - 8, 9 - 12, 13 - 16, 17 - 20, or 21 - 24 weeks were associated with a higher likelihood of achieving pCR compared with ≤ 4 weeks (34). In patients without pCR, delaying surgery for more than 12 weeks was associated with reduced OS. In the current study, all the patients underwent surgery about 6 - 8 weeks after CRT, and there is no difference between those with pCR and those who did not achieve pCR.

In this study tumor location did not significantly influence pCR rates, though lower rectum tumors showed a non-significant trend toward better response. This observation aligns with some studies suggesting that lower rectal tumors might be more susceptible to effective CRT (35).

We must acknowledge some limitations. First, the study's retrospective design inherently limits the ability to establish causality between the examined variables and observed outcomes. Prospective studies are needed to confirm the predictive value of the identified factors and more effectively account for potential confounding variables.

Moreover, the study did not investigate molecular or genetic markers, which are increasingly recognized as important factors in predicting response to therapy. Incorporating these biomarkers into future research could provide a more comprehensive understanding of the factors influencing pathological response for personalized treatment strategies.

Furthermore, this cross-sectional study did not include follow-up on patients' long-term outcomes — such as overall and disease-free survival. Future long-term follow-up studies are necessary to confirm the prognostic relevance of pCR and to further elucidate its role in long-term treatment management.

5.1. Conclusions

This study found that clinical stage and the extent of induction chemotherapy are critical predictors of pCR in patients with LARC. These findings emphasize the importance of initial tumor staging and the potential benefit of more intensive chemotherapy regimens in achieving better outcomes.

Footnotes

Authors' Contribution: Study concept and design: A. R.; Acquisition of data: F. Sh.; Analysis and interpretation of data: M. K. Kh. and F. Sh.; Drafting of the manuscript: M. K. Kh.; Critical revision of the manuscript for important intellectual content: A. R.

Conflict of Interests Statement: The authors declared no conflict of interests.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: The protocol of the study was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.201). This research was carried out in line with the Helsinki Declaration.

Funding/Support: The authors declare that they did not receive any funding for this study.

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