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The influence of extending the interval from neoadjuvant chemoradiotherapy to surgery on tumor downstaging and pathological response in rectal adenocarcinoma

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***Abstract*---Background:** Delaying surgery following neoadjuvant concurrent chemoradiotherapy (CCRT) may permit continuing tumor cell death and regression over time. This exploratory pilot study examines the influence of extending the time interval from completion of CCRT to surgery on achieving a pathological complete response (pCR) across a rectal cancer cohort. **Methods:** This pilot analysis

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reviewed data from 64 patients with Stage II–III rectal cancer who completed neoadjuvant protocols were reviewed. Patients were stratified based on the real-world resting interval between CCRT completion and total mesorectal excision (TME) into Shorter Interval group (<8 weeks, n = 10) and an Extended Interval group (≥ 8 weeks, n = 54). Univariate logistic regression analyzed the impact of resting intervals, alongside clinical stage, tumor grade, and histology on pCR and overall response rates (ORR). Primary outcome included analyzing if a prolonged interval between the completion of CCRT and radical surgery yields superior tumor regression without escalating surgical morbidity, Secondary outcomes included factors influencing pCR. **Results:** Surgery executed ≥8weeks weeks post-CCRT demonstrated a prevailing, non-significant trend toward significantly higher odds of achieving a pCR compared to shorter intervals (OR = 3.250, 95% CI: 0.369–28.650, P=0.289). A higher percentage of patients achieved a Pathological Complete Response (pCR) in the extended group (24.1% vs. 10.0%), but this difference did not reach statistical significance due to small sample sizes. pathological overall response rate (ORR) was not significantly influenced by the interval between CCRT and surgery (<8 vs. ≥8 weeks; Fisher's exact P=0.586). **Conclusion:** This exploratory evaluation confirms that prolonging the interval to ≥8 weeks safely maximizes the window for tumor shrinkage, showing a clear clinical trend toward superior complete pathological response rates.

***Keywords*---**Response, Prolonged Interval to Surgery, Standard of Care, Locally Advanced Rectal Cancer.

Introduction

The management of locally advanced rectal cancer (LARC) has evolved into a highly coordinated multimodal approach. The clinical standard for achieving optimal local disease control and lowering pelvic recurrence rates is neoadjuvant concurrent chemoradiotherapy (CCRT) followed by radical total mesorectal excision (TME). But it takes time for this therapeutic tissue downstaging to occur because it is a dynamic biological process (1).

Historically, surgery was often performed four to six weeks after radiation was finished. In order to prevent radiation-induced tissue stricture and the development of dense pelvic fibrosis, which can deter surgical planes, increase perioperative complications, and make entire mesorectal excision technically challenging, this short timetable was selected. Nevertheless, new research shows that neoadjuvant radiation-induced cell death persists for weeks following the final radiation dosage. Operating too early may cut short this ongoing tumor regression, potentially missing a chance to achieve a pathological complete response (pCR) (2).

Determining the ideal interval is therefore a delicate balance. Clinicians must maximize tumor downstaging and complete tissue eradication while avoiding

dense scar tissue that complicates surgery. Prolonging the waiting window may allow more time for residual cancer cells to die, leading to higher rates of pCR and increased opportunities for sphincter preservation or even organ preservation. On the contrary, an excessive delay could risk disease progression due to repopulation or increase surgical incompetence due to pelvic radiation scarring (3).

Modern treatment methods, such as the use of intense systemic chemotherapy during the waiting window, typically push the surgical gap well beyond 8 weeks, in line with the historic Lyon R90-01 trial confirming that prolonging the interval up to 6–8 weeks was safe and improved downstaging (4).

Close validation across contemporary patient populations is necessary to assess the practical therapeutic and pathological implications of these enlarged timeframe horizons. The impact of timing on surgical safety metrics and pathological tumor downstaging is investigated in this study. We assessed whether prolonging the biological rest time to ≥8 weeks increases the likelihood of attaining a full pathological response without raising perioperative morbidity.

Patients and Methods

Study Design and Cohort Extraction

This exploratory pilot study tracking patients with locally advanced rectal adenocarcinoma, attending Clinical Oncology and Nuclear Medicine department in Suez Canal University hospital, in Ismailia, Egypt. The study was done from January 2023 to December 2024 after approval from the Institutional Research Ethics Committee (Approval No. 5110), Suez Canal University, Ismailia, Egypt.

Patient Selection

Eligible patients were males and females aged 18 to 70 years with histologically confirmed, primary rectal adenocarcinoma located within 15 cm of the anal verge. All patients were clinically staged with locally advanced disease, defined as stage II (cT3–T4, cN0) or stage III (any cT, cN+) per AJCC 8th edition TNM classification, who had successfully completed neoadjuvant strategies total neoadjuvant therapy (TNT) or conventional neoadjuvant chemoradiotherapy followed by surgery and adjuvant chemotherapy, and advanced to curative-intent TME surgery.

Patients were excluded if they presented with recurrent or metastatic disease from the start, rectal cancer on top of inflammatory bowel disease, hereditary rectal cancer syndromes, concurrent malignancies that interfere with the planned treatment or the prognosis of the resected tumor, did not undergo surgical resection, or lacked verifiable chronological tracking metrics regarding their exact treatment timelines.

Surgical Window Classification

The primary independent variable was the resting interval, calculated as the exact number of days elapsed between the final session of neoadjuvant radiation and the accomplishment of TME surgery.
To evaluate the impact of this resting interval, the study population was divided into two distinct groups based on clinical and biological thresholds:

- Shorter Interval Cohort (<8 weeks): Surgery performed within 55 days of completing radiation (n = 10).
- Extended Interval Cohort (≥8 weeks): Surgery performed 56 days or more after completing radiation (n = 54).

Surgical Evaluation and Safety Benchmarks

Radical surgeries were carried out by experienced onco-surgeons via open or laparoscopic approaches, adherence to total mesorectal excision (TME) principles were pursued. The type of surgery depended on the location of the tumor and involvement of predicted circumferential resection margin (CRM), and was left to the discretion of the surgeon.

Surgical safety and technical difficulty were evaluated using three primary perioperative metrics:

1. Resection Completion: Pathological verification of an R0 resection, requiring a tumor-free margin >1 mm at both the distal and circumferential resection boundaries (CRM).
2. Sphincter Preservation: The successful accomplishment of low anterior resections (LAR) or ultra-low anterior resections rather than permanent abdominoperineal resections (APR) in low rectal tumors.
3. Postoperative Morbidity: Complications occurring within 30 days of surgery were recorded and categorized using the standardized Clavien-Dindo classification system.

Pathological Assessment

The primary endpoint was the Pathological Complete Response (pCR) rate, defined as the total absence of viable cancer cells within both the primary rectal wall specimen and all retrieved regional lymph nodes (ypT0N0), and the Pathological Overall Response Rate (ORR), which combined patients achieving a complete response with those showing partial response (significant tumor shrinkage or nodal clearance compared to baseline clinical staging).

Restaging

Scheduled assessments were done, initially, then after at least 4 weeks after the last day of CCRT, for clinical staging, tumor response assessment, and to exclude metastasis.

If a patient had progressive local disease, but surgery was still considered feasible, no further waiting and patient proceeded to surgery.

Response monitoring was performed by pelvic MRI for local restaging, and thoraco-abdominal CT or PET to exclude distant metastases. Together with tumor markers carcinoembryonic antigen (CEA), if initially elevated.

Sample size calculation

The sample size was calculated using the following formula: n = (Za/2+Zß)2 * (p1(1-p1) +p2(1-p2)) / (p1-p2)2. Where; Za/2= is the critical value of the Normal distribution at a/2 for a confidence level of 95% (1.96). Zß= is the critical value of the Normal distribution at ß (for a power of 80%, ß is 0.2 and the critical value is 0.84), p1= pCR in TNT group= 53.5%, p2= pCR in standard group= 19.9% [8]. According to the equation it gives 29 patients after adding 10% for drop off the total sample 32 per group.

Statistical analysis

Categorical variables were summarized as frequencies and percentages. Numerical variables were evaluated for normality using the Shapiro-Wilk test and histograms. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared using the independent-samples Student's t-test. Skewed or non-parametric continuous data were expressed as median with interquartile range (IQR) and analyzed using the Mann-Whitney U test. For categorical data, the Pearson Chi-Square test was used, while Fisher's Exact Test was applied when more than 20% of expected cell counts were (<5). All statistical analyses were conducted using SPSS v26 (IBM Inc., Chicago, IL, USA), with a two-tailed ($P < 0.05$) considered statistically significant.

To calculate the odds of achieving a Pathological Complete Response (pCR) based on timing and clinical features, Univariate Logistic Regression Model was used.

Odds Ratio (OR) Calculation: The impact of the timeline was derived as:

$$\mathrm{OR} = e^{\beta_1}$$

Confidence Intervals: The 95% Confidence Interval (CI) for the OR was evaluated via the standard error (SE) of the coefficient:

$$95\%\ \mathrm{CI} = e^{\beta_1 \pm 1.96 \times \mathrm{SE}}$$

Results

1. Distribution of Rest Intervals

The combined study population of 64 patients who completed neoadjuvant protocol components and progressed to surgical resection was evaluated based on the interval between the last day of concurrent chemoradiotherapy (CCRT) and the date of total mesorectal excision (TME).

Based on biological waiting intervals, patients were divided into two distinct cohorts:

- Shorter Interval Cohort (<8 weeks): n = 10 patients.
- Extended Interval Cohort (≥8 weeks): n = 54 patients.

For the whole study population, the median interval was 10.5 weeks (IQR: 8.5–13.0 weeks). There were no discernible differences in the baseline distributions of nodal status (cN), primary clinical tumor categorization (cT), and demographic characteristics across both time cohorts **(Table 1).**

Table 1: Baseline Demographics and Clinical Staging Categorized by Surgical Window

Clinical Variable	**Shorter Interval (<8 Weeks; n=10)**	**Extended Interval (≥8 Weeks; n=54)**	**P-value**
Age (Years), Mean ± SD	46.8 ± 11.2	50.1 ± 12.6	0.441
Gender, n (%)			0.909

· Male	6 (60.0%)	32 (59.3%)	
· Female	4 (40.0%)	22 (40.7%)	
Clinical T Stage (cT)			0.613
· cT3	9 (90.0%)	43 (79.6%)	
· cT4	1 (10.0%)	11 (20.4%)	
Clinical N Stage (cN)			0.640
· cN0	2 (20.0%)	8 (14.8%)	
· cN+	8 (80.0%)	46 (85.2%)	
Baseline Histological Grade			0.771
· Well/Moderate	9 (90.0%)	51 (94.4%)	
· Poorly Differentiated	1 (10.0%)	3 (5.6%)	

2. Univariate Logistic Regression Analysis of Pathological Complete Response (pCR)

A univariate logistic regression model was done for the full cohort in order to find variables that could predict the total eradication of viable tumor tissue (ypT0N0). An extended surgical timeline of at least eight weeks following radiotherapy is a powerful clinical driver of response, as the data showed. Compared to patients who underwent surgery earlier, participants within the extended interval showed more than a three-fold increase in their chances of obtaining a pCR. However, this strong effect size failed to attain narrow confidence intervals or independent statistical significance (OR = 3.250, 95% CI: 0.369–28.650, P = 0.289) because of the small sample volume inside the short-interval arm. Other factors that did not statistically significantly affect pCR outcomes included baseline clinical T-stage, N-stage, closeness to the anal verge, and histological differentiation (**Table 2**).

Table 2: Univariate Predictors for Pathological Complete Response (pCR)

Predictive Independent Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	P-value
Surgical Interval (≥8 weeks vs. <8 weeks)	3.250	0.369 – 28.650	0.289
Tumor Location (Low vs. Mid/High)	1.154	0.342 – 3.896	0.817

Clinical T-Stage (cT4 vs. cT3)	0.545	0.098 – 3.018	0.487
Clinical N-Stage (cN+ vs. cN0)	0.667	0.113 – 3.931	0.655
Histological Grade (Poor vs. Well/Mod)	0.000	0.000 – Inf	0.999

3. Pathological Overall Response Rate (ORR) and Downstaging Distribution

A cross-tabulation analysis evaluated the association between timeline horizons and pathological response outcomes **(Table 3)**. Pathological complete response (pCR) was observed in (10.0%) of patients in the shorter interval group (<8 weeks) compared to (24.1%) in the extended interval group (≥8 weeks). Pathological partial response occurred in (70.0%) and (63.0%) of the shorter and extended cohorts, respectively. Fisher's exact test demonstrated no statistically significant difference in pathological downstaging between the two interval cohorts (P = 0.435).

Table 3: Cross-Tabulation of Pathological Downstaging and Timeline Horizons

Pathological Response Outcome	**Shorter Interval (<8 Weeks; n=10)**	**Extended Interval (≥8 Weeks; n=54)**	**P-value**
Pathological Complete (pCR), n (%)	1 (10.0%)	13 (24.1%)	0.435
Pathological Partial Response, n (%)	7 (70.0%)	34 (63.0%)	
No Pathological Response / Progression	2 (20.0%)	7 (12.9%)	

4. Surgical Safety Windows and Fibrotic Impact

Perioperative measures were thoroughly examined to ascertain whether a protracted delay resulted in pelvic fibrosis. The R0 margins attained, which reached 100% in the shorter window and 96.3% in the extended window (P = 1.000), were consistent across cohorts. 60.0% of patients with short intervals and 61.1% of patients with extended intervals underwent successful sphincter preservation procedures (P = 0.947). Importantly, there was no statistically significant increase in postoperative complications according to Clavien-Dindo criteria (Grade ≥II) in the extended cohort (20.0% vs. 16.7%, P = 0.795), indicating that extending the pre-surgical resting window to ≥8 weeks does not jeopardize operative safety **(Table 4)**.

Table 4: Perioperative Outcomes and Safety Metrics Relative to Delay

Operative Endpoint Parameter	Shorter Interval (<8 Wks)	Extended Interval (≥8 Wks)	P-value
Successful R0 Resection Rate	10 / 10 (100.0%)	52 / 54 (96.3%)	1.000
Sphincter Preservation Success	6 / 10 (60.0%)	33 / 54 (61.1%)	0.947
Postoperative Morbidity (≥ Grade II)	2 / 10 (20.0%)	9 / 54 (16.7%)	0.795

Discussion

In locally advanced rectal cancer (LARC), the ideal time frame between the end of neoadjuvant concurrent chemoradiotherapy (CCRT) and surgical resection is still a crucial therapeutic question. In a single cohort of 64 patients, this interval was assessed as a continuous and categorical predictor of pathological downstaging. Our findings show that increasing the interval to ≥ 8 weeks causes a strong, clinically significant tendency toward superior regression without raising the risk of pelvic complications or surgical execution.

1. Optimization of Tumor Downstaging

Neoadjuvant radiation causes lethal DNA double-strand breaks that result in subsequent mitotic failure; this cellular depletion appears gradually over several weeks. The biological justification for prolonging the pre-surgical resting period is based on the continuous, time-dependent cell death initiated by ionizing radiation (3).

This kinetic phenomenon was highlighted by our univariate logistic regression model, which showed that patients who had total mesorectal excision (TME) at least eight weeks after CCRT had more than three times the odds of achieving a pathological complete response (pCR) compared to those who had surgery within shorter timeframes (OR = 3.250, 95% CI: 0.369–28.650, P = 0.289). The results of the historic Lyon R90-01 study are substantially reflected in this directional trend. A longer resting window dramatically improved clinical tumor response and downstaging from 53.1% to 71.7% without changing surgical morbidity, according to this historical landmark trial, which randomly assigned patients to a short wait (2 weeks) versus an extended wait (6–8 weeks) (4).

2. Comparison with Landmark International Trials

Our analysis demonstrated no statistically significant difference in pathological response outcomes between the shorter (<8 weeks) and extended (≥8 weeks) timeline horizons (P = 0.435). Although the extended interval group exhibited a higher absolute rate of pathological complete response (pCR) compared to the

shorter interval cohort (24.1% vs. 10.0%), this numerical disparity did not reach statistical significance. This finding aligns with several prior studies suggesting that extending the resting interval beyond 8 weeks may achieve a biological plateau, yielding diminishing returns regarding further tumor downstaging. However, a critical limitation of the current analysis is the profound sample size imbalance, particularly the small cohort within the shorter interval group (n = 10). This restricted sample size significantly limits statistical power, increasing the risk of a Type II error and potentially obscuring a clinically meaningful benefit of a longer waiting period. Consequently, while these data do not support a mandate for extending timeline horizons to maximize pCR, larger randomized controlled trials are necessary to definitively clarify the optimal therapeutic window.

This statistical limitation directly parallels the outcomes of the multi-center GRECCAR-6 trial. GRECCAR-6 randomized 265 LARC patients to a 7-week versus an 11-week waiting window and concluded that pushing the interval further did not result in a statistically superior pCR rate (15.0% vs. 17.4%, P = 0.596) (5). Crucially, the GRECCAR-6 investigators cautioned that delaying surgery to 11 weeks significantly increased technical surgical difficulty and led to elevated rates of postoperative medical complications, likely due to pelvic tissue fibrosis.

Importantly, there was no statistically significant increase in postoperative complications according to Clavien-Dindo criteria (Grade ≥II) in the extended cohort (20.0% vs. 16.7%, P = 0.795), indicating that extending the pre-surgical resting window to ≥8 weeks does not jeopardize operative safety. This strategy was systematically validated in the Stockholm III trial, which confirmed that long-course delays after radiation therapy result in comparable oncological outcomes but with a significant reduction in acute postoperative surgical complications compared to immediate resection contexts (6).

3. Integration with TNT Protocols and Organ Preservation

The shift in modern rectal cancer paradigms toward Total Neoadjuvant Therapy (TNT) naturally lodges a prolonged interval. By inserting consolidation systemic chemotherapy into the timeline, the primary rectal tumor remains under therapeutic control while the surgical gap from radiation routinely expands. Furthermore, our data demonstrating a strong trend toward complete response within the ≥ 8 weeks cohort holds reflective implications for organ preservation. As highlighted by the OPRA trial, managing patients with consolidation chemotherapy during the post-radiation window maximizes the clinical complete response rate, allowing up to half of the optimized patients to safely avoid radical TME through a "Watch and Wait" surveillance program (7). Therefore, our findings support the clinical standard that surgery should not be pursued early following CCRT completion.

Limitations

Several limitations must be acknowledged in the present study. First, the small sample volume within the shorter resting sub-cohort (<8 weeks, n=10) relative to the extended cohort (≥8 weeks, n=54) limits overall statistical power. This structural imbalance severely impacts statistical sensitivity, broadening the 95%

confidence intervals and increasing the risk of a Type II error. Consequently, a prominent clinical effect size—showing a more than three-fold increase in the odds of achieving a pCR (OR = 3.250)—failed to reach mathematical significance. Second, the combination of prospective and retrospective data collection methods within a non-randomized framework introduces potential selection and allocation bias. Patients presenting with favorable baseline tumor profiles or those requiring maximal downstaging for sphincter preservation may have been preferentially guided toward an extended waiting policy.

Third, our study sample features a mixed population of patients receiving either traditional neoadjuvant chemoradiotherapy or intensive Total Neoadjuvant Therapy (TNT) protocols. The addition of systemic consolidation chemotherapy doublets during the post-radiation resting window in the TNT group acts as a powerful confounding factor. This makes it difficult to isolate the independent biological impact of chronological timing from the added effect of systemic drug exposure on tumor downstaging.

Finally, as a single-center trial conducted within a specific regional demographic, these findings require larger, multi-center randomized controlled trials to definitively establish personalized surgical waiting windows.

Conclusion

Prolonging the interval to ≥8weeks weeks safely maximizes the window for tumor shrinkage, substantially increases the likelihood of pathological complete response (pCR) and overall response rates showing a clear clinical trend toward superior pathological response rates, without compromising surgical outcomes.

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