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Total Neoadjuvant Treatment in Locally Advanced Rectal Cancer: A Comparative Study of PRODIGE 23 versus RAPIDO Protocols

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Abstract

Background: Total neoadjuvant treatment (TNT) has significantly transformed the management of locally advanced rectal cancer (LARC). The PRODIGE 23 and RAPIDO trials introduced new strategies in TNT, demonstrating improved complete pathological response (pCR) rates and relapse-free survival. **Objective:** To compare clinical outcomes, toxicities, and response rates in patients treated with the PRODIGE 23 and RAPIDO TNT protocols. **Methods:** A retrospective, analytical study was conducted including 48 patients with LARC treated between January 2021 and December 2023 at CHU Hassan II of Fez. Patients were treated according to either the PRODIGE 23 or RAPIDO protocol. Clinical characteristics, treatment response, toxicities, and survival outcomes were compared. **Results:** The median age was 55.3 years, with 56.3% male patients. Most tumors were located in the mid-rectum, and all patients had adenocarcinoma. TNT was administered per PRODIGE 23 in 56.3% and RAPIDO in 43.8%. T4 tumors were more frequent in the PRODIGE 23 group (66.6% vs. 47.6%), although this difference was not statistically significant ($p = 0.14$). Nodal involvement was present in nearly all cases. The overall rate of grade ≥3 toxicities was 12.5%. The most common severe adverse events were neutropenia (14.6%), asthenia (8.3%), and anemia (6.3%). Pathological complete response was significantly higher with PRODIGE 23 (22.2%, $p = 0.028$). Median relapse-free, metastasis-free, and overall survival were 14.52, 14.98, and 21.83 months, respectively, with improved outcomes in the PRODIGE 23 group. **Conclusion:** PRODIGE 23 appears to offer superior pathological and survival outcomes compared to RAPIDO. Future prospective studies should aim to personalize TNT strategies and identify patients who would benefit most from treatment intensification or de-escalation.

Keywords

Locally Advanced Rectal Cancer, Total Neoadjuvant Treatment, PRODIGE 23, RAPIDO, Induction Chemotherapy, Consolidation Chemotherapy, Pathological Complete Response, Survival

1. Introduction

Locally advanced rectal cancer (LARC) poses significant therapeutic challenges due to its risk of both locoregional recurrence and distant metastasis [1]. Total neoadjuvant treatment (TNT), combining chemotherapy and chemoradiotherapy prior to surgery, has emerged as a promising approach to optimize disease control [2] [3].

Two major clinical trials, RAPIDO and PRODIGE 23, published in 2021, have contributed to redefining treatment paradigms. The RAPIDO trial emphasized short-course radiotherapy followed by consolidation chemotherapy, whereas the PRODIGE 23 trial introduced induction chemotherapy with mFOLFIRINOX followed by chemoradiation [4] [5].

This study aimed to compare the two TNT strategies in a real-world cohort to evaluate their respective impacts on tumor response, toxicity, and survival.

2. Materials and Methods

2.1. Study Design and Population

A retrospective, comparative study was conducted including 48 patients with histologically confirmed LARC treated at the Medical Oncology Department of CHU Hassan II, Fez, from January 2021 to December 2023.

2.2. Inclusion Criteria

Patients were eligible if they were ≥18 years old, had an ECOG performance status of 0 - 2, clinical stage cT3-T4 and/or N+, no distant metastases, and completed TNT per PRODIGE 23 or RAPIDO protocols with full clinical, radiological, and pathological data available.

2.3. Exclusion Criteria

Exclusion criteria included metastatic disease at diagnosis, prior pelvic radiotherapy, incomplete TNT, or missing follow-up data.

2.4. Treatment Protocols

PRODIGE 23 consisted of induction mFOLFIRINOX (6 cycles) followed by long-course chemoradiotherapy (50.4 Gy/28 fractions with concurrent capecitabine) and surgery.

RAPIDO involved short-course radiotherapy (5 × 5 Gy) followed by consolidation chemotherapy (Xelox or FOLFOX, 6 cycles) and surgery.

2.5. Endpoints and Definitions

Primary endpoint: pCR (ypT0N0).

Secondary endpoints: relapse-free survival (RFS), metastasis-free survival (MFS), overall survival (OS), and grade ≥3 toxicity (CTCAE v5.0).

Follow-up was calculated from TNT initiation to recurrence or death.

2.6. Data Collection

We collected demographic data, tumor location, histology, staging, treatment details, chemotherapy regimens, cycles, treatment-related toxicities (graded by CTCAE v5.0), radiological and pathological responses, type of surgery, and survival outcomes.

2.7. Statistical Analysis

Descriptive statistics summarized patient characteristics. Chi-square or Fisher's exact tests were used for categorical variables, and t-tests for continuous variables. Survival was analyzed using the Kaplan-Meier method with log-rank tests. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics

The median age of the study population was 55.3 years (range: 24 - 84), with 56.3% being male. In the PRODIGE 23 group (n = 27), T4 tumors were present in 66.6% of patients, with nodal involvement observed in 96.2%. In comparison, the RAPIDO group (n = 21) had T4 tumors in 47.6% of cases and nodal involvement in 100% (Table 1). The higher T4 rate in PRODIGE 23 was not statistically significant ($p = 0.14$). Most tumors were located in the mid-rectum (79.2%), and all were adenocarcinomas.

Table 1. Baseline clinical and pathological characteristics of the two treatment groups.

Characteristic	PRODIGE 23 (n = 27)	RAPIDO (n = 21)	p-value
Median age (years)	54.8	55.9	0.72
Male sex (%)	59.2	52.3	0.58
T4 stage (%)	66.6	47.6	0.14
Nodal involvement (%)	96.2	100	0.39

3.2. Treatment and Toxicity

Within the PRODIGE 23 cohort, mFOLFIRINOX was used as induction chemotherapy in 57.2% of patients, whereas in the RAPIDO cohort, Xelox was administered as consolidation therapy in 27.1% of cases. The mean number of chemotherapy cycles across the study population was six, ranging from two to nine.

Grade ≥3 toxicities were observed in 12.5% of patients overall (Table 2). The most frequent severe adverse event was neutropenia (14.6%), followed by asthenia

(8.3%) and anemia (6.3%). Hand-foot syndrome and allergic reactions each occurred in 2.1% of patients. Radiotherapy-related toxicities were mostly grade 1, including diarrhea (10.4%), proctitis (12.5%), and radiodermatitis (12.5%). No patient discontinued treatment due to toxicity.

Surgery was performed approximately 9 weeks after TNT completion for both groups, predominantly via anterior rectal resection.

3.3. Pathological and Survival Outcomes

The overall pathological complete response (pCR) rate was 25%, with a significantly higher rate in the PRODIGE 23 group compared to RAPIDO (22.22% vs 19.02%, p = 0.028). Median relapse-free survival (RFS) was 14.52 months, metastasis-free survival (MFS) was 14.98 months, and overall survival (OS) was 21.83 months. All three survival metrics favored the PRODIGE 23 group, with OS showing statistical significance (p = 0.004). (Table 2)

Table 2. Treatment outcomes and toxicity profiles for both groups.

Outcome Measure	PRODIGE 23	RAPIDO	p-value	95% CI
pCR (%)	22.22	19.02	0.028	0.30 - 5.19
OS (months)	21.76	20.70	0.004	0.01 - 0.60
RFS (months)	16.00	13.71	0.061	—
MFS (months)	14.70	14.28	0.030	1.00 - 6.20
Grade ≥3 toxicity (%)	8.67	3.87	0.21	—

pCR = pathological complete response; OS = overall survival; RFS = relapse-free survival; MFS = metastasis-free survival; CI = confidence interval.

4. Discussion

This comparative study between two total neoadjuvant treatment (TNT) protocols-PRODIGE 23 and RAPIDO-in patients with locally advanced rectal cancer (LARC) highlights the clinical benefits of intensified induction chemotherapy. Our findings confirm that the PRODIGE 23 protocol is associated with a significantly higher pathological complete response (pCR) rate and improved relapse-free survival (RFS), metastasis-free survival (MFS), and overall survival (OS) compared to the RAPIDO protocol.

The observed benefits in the PRODIGE 23 group may be attributed to the early administration of intensified systemic chemotherapy (mFOLFIRINOX), which likely enhances control of micrometastatic disease prior to surgery [3] [4] [6] [7]. This approach aligns with current biological hypotheses suggesting that systemic therapy is more effective when delivered before surgery, while tumor vasculature remains intact and drug delivery is optimized. Moreover, TNT with induction chemotherapy facilitates better adherence to systemic therapy, which is often under-delivered in the adjuvant setting due to postoperative morbidity and patient fatigue [7] [8].

In our study, the overall pCR rate was 25%, with a significantly higher rate in

the PRODIGE 23 group (22.22% vs. 19.02%, p = 0.028). This finding is consistent with the original PRODIGE 23 trial, which reported a pCR rate of 27.5% [4]. In contrast, the RAPIDO protocol [5]-although based on short-course radiotherapy followed by consolidation chemotherapy-appeared less effective in our cohort. This may be due to the lower intensity of systemic chemotherapy (Xelox in 27.1% of cases) and potentially less favorable patient characteristics.

When comparing our cohort with the original RAPIDO and PRODIGE 23 trials (**Table 3**), several differences in baseline characteristics and pathological outcomes become apparent. Patients in our study were generally younger, with a mean age of 53.7 years in the RAPIDO arm and 57.3 years in the PRODIGE 23 arm, compared with 62 and 61 years, respectively, in the original trials. The distribution of tumor stages also varied: in our RAPIDO arm, T3 tumors accounted for 52.38% of cases compared with 65% in the RAPIDO trial, while T4 tumors were more frequent (47.61% vs. 32%). Similarly, in the PRODIGE 23 arm, T3 tumors were less common in our cohort (33.33% vs. 81%), whereas T4 tumors were more frequent (66.66% vs. 18%). Nodal involvement (N+) was observed in all patients in our RAPIDO arm (100%) and in 96.29% of the PRODIGE 23 arm, slightly exceeding the rates reported in the respective trials (91% and 90%).

Regarding survival outcomes, our RAPIDO arm showed lower OS at 71.42% compared with 89.1% in the original RAPIDO trial, while our PRODIGE 23 arm achieved 81.48% versus 90.8% in the original trial. Conversely, MFS was higher in our cohort-90.47% in the RAPIDO arm and 92.59% in the PRODIGE 23 arm-compared with 80% and 78.8% in the original trials. RFS in our study was slightly lower in the RAPIDO arm (85.71% vs. 91.3%) but similar in the PRODIGE 23 arm (92.59% vs. 95.2%). pCR rates were lower in both arms of our study-19.02% in RAPIDO and 22.22% in PRODIGE 23-compared with 28.4% and 27.5% reported in the original trials. These differences may reflect variations in patient selection, tumor biology, treatment delivery, or supportive care measures between our real-world cohort and the populations included in the pivotal trials.

Table 3. Baseline characteristics and pathological outcomes in RAPIDO, PRODIGE 23 trials, and the present study.

Characteristic	RAPIDO Trial	PRODIGE 23 Trial	Present Study-RAPIDO	Present Study-PRODIGE 23
Mean age (years)	62	61	53.7	57.3
T3 (%)	65.0	81.0	52.38	33.33
T4 (%)	32.0	18.0	47.61	66.66
N+ (%)	91.0	90.0	100.0	96.29
OS (%)	89.1	90.8	71.42	81.48
MFS (%)	80.0	78.8	90.47	92.59
RFS (%)	91.3	95.2	85.71	92.59
pCR (%)	28.4	27.5	19.02	22.22

OS, overall survival; MFS, metastasis-free survival; RFS, relapse-free survival; pCR, pathological complete response; N+, node-positive disease.

The younger age observed in our cohort could be attributed to demographic differences and referral patterns within our institution, potentially influencing treatment tolerance and long-term prognosis. However, the markedly higher proportion of T4 tumors in both arms of our study suggests a more advanced local disease burden at baseline, which may partially explain the lower pCR and OS rates compared with the original trials. Advanced T-stage is known to be associated with more aggressive tumor biology, increased likelihood of positive margins, and reduced responsiveness to neoadjuvant therapy. In contrast, the higher MFS rates in our cohort, particularly in the PRODIGE 23 arm, may indicate effective systemic disease control despite the high local tumor stage, possibly reflecting improvements in multidisciplinary management, chemotherapy delivery, and follow-up strategies in our setting. These findings underscore the importance of tailoring trial protocols to the specific characteristics of real-world populations, as variations in baseline staging and treatment sequencing can significantly influence outcome interpretation.

Toxicity analysis revealed that, while PRODIGE 23 involves a more intensive regimen, treatment-related adverse events remained manageable. Grade ≥3 toxicities, mainly hematologic and gastrointestinal, were more frequent in the PRODIGE 23 group but did not lead to treatment discontinuation. These results are in line with the literature, which supports the feasibility of mFOLFIRINOX in carefully selected patients with appropriate supportive care [8] [9].

Locoregional and metastatic recurrence rates were higher in the RAPIDO group, although not statistically significant. This trend reinforces the potential role of early systemic intensification in reducing tumor dissemination and improving long-term disease control [10].

Future Directions To strengthen clinical decision-making, molecular biomarkers should be integrated into TNT strategies. Microsatellite instability (MSI) and RAS/BRAF mutations are clinically relevant, as MSI-high tumors may benefit from immunotherapy, while RAS/BRAF mutations influence prognosis and therapeutic sensitivity. Incorporating molecular stratification could help optimize patient selection for intensification or de-escalation of TNT.

Innovations such as ctDNA monitoring [11], advanced imaging, and radiomics [7] [12] may further personalize treatment, supporting "watch-and-wait" strategies or treatment adaptation in selected patients.

The integration of these innovations, alongside robust postoperative surveillance programs [13], will be critical to tailoring therapy to individual patient profiles and maximizing long-term outcomes.

Limitations of the Study

This study has several limitations that should be considered when interpreting the findings. First, its retrospective design inherently carries a risk of selection and information bias. Second, the relatively modest sample size limits statistical power and reduces the reliability of subgroup analyses. Third, treatment implementation was not entirely uniform and may have deviated from the strict protocols used in

landmark trials, potentially influencing outcomes. Fourth, the absence of molecular biomarker data—such as microsatellite instability (MSI) or RAS/BRAF mutation status—restricted our ability to perform more refined prognostic or predictive stratifications. Finally, the relatively short follow-up period precludes a comprehensive assessment of long-term survival outcomes.

5. Conclusion

Our findings support the adoption of intensified total neoadjuvant therapy (TNT) with induction chemotherapy, as exemplified by the PRODIGE 23 protocol, in patients with locally advanced rectal cancer (LARC). Compared to the RAPIDO regimen, PRODIGE 23 was associated with higher pathological complete response rates and superior survival outcomes. Moving forward, clinical efforts should aim to refine patient selection criteria for TNT intensification or de-escalation, while incorporating molecular profiling and advanced response assessment tools—such as circulating tumor DNA and functional imaging—into routine decision-making to further personalize treatment strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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