Society of Medical Education & Research

2025, Volume 5, Issue 1, Page No: 40-52

ISSN: 3108-4834

Archive of International Journal of Cancer and Allied Science

Total Neoadjuvant Therapy versus Neoadjuvant Chemoradiotherapy and Adjuvant Chemotherapy in Locally Advanced Rectal Cancer: Comparable Survival with Enhanced Tumor Response

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Abstract

Total neoadjuvant therapy (TNT) enhances tumor regression in individuals with locally advanced rectal cancer (LARC) relative to standalone neoadjuvant chemoradiotherapy. The influence of TNT on overall patient outcomes remains incompletely explored. This retrospective review involved cases of LARC managed at a major oncology facility. A group of 311 patients underwent chemoradiotherapy (chemoRT) exclusively as neoadjuvant therapy, with scheduled postoperative chemotherapy, while 313 patients were treated with TNT, consisting of upfront chemotherapy based on fluorouracil and oxaliplatin followed by chemoradiotherapy prior to surgery. Subsequently, participants proceeded to total mesorectal excision or enrollment in a watch-and-wait strategy. Complete response (CR) rates post-neoadjuvant treatment—defined as pathologic CR or sustained clinical CR for 2 years—were evaluated using the χ^2 test. Kaplan-Meier curves with log-rank testing were applied to analyze disease-free survival (DFS), local recurrence-free survival, distant metastasis-free survival, and overall survival. Additional assessment of DFS employed Cox proportional hazards models. Complete response occurred in 20% of chemoRT cases versus 27% in the TNT arm (P=.05). No significant differences emerged in DFS, local recurrence-free survival, distant metastasis-free survival, or overall survival. The neoadjuvant approach did not impact disease-free survival (hazard ratio [HR] 1.3; 95% confidence interval [CI] 0.93-1.80; P = .12). TNT fails to extend survival beyond that achieved with neoadjuvant chemoradiotherapy combined with planned adjuvant chemotherapy; nevertheless, its superior response rates could enable organ preservation in a greater number of LARC cases.

Keywords: Total neoadjuvant therapy, Survival, Response, Locally advanced rectal cancer

Introduction

Preoperative chemoradiotherapy combined with total mesorectal excision (TME) effectively controls local disease in locally advanced rectal cancer (LARC) [1, 2]. Regrettably, distant metastases develop in more than 25% of those receiving chemoradiotherapy and TME, representing the primary fatal complication [2, 3]. Drawing from advantages seen in colon cancer management, systemic adjuvant chemotherapy is advised for LARC patients following chemoradiotherapy and intended curative TME [4]. Yet, its definitive advantages remain unestablished [5, 6].

A meta-analysis encompassing 21 randomized studies reported improved disease-free survival (DFS) and overall survival with postoperative chemotherapy versus observation after definitive resection [7]. These findings faced scrutiny due to inclusion of suboptimal TME techniques and cases involving postoperative chemoradiotherapy [8]. An updated individual-patient-data meta-analysis from 4 randomized trials indicated no survival gain from adjuvant fluorouracil-based regimens in mid- or low-rectal tumors managed with preoperative

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Received: 12 December 2024; **Accepted:** 04 March 2025

How to cite this article: Ben Salem NL, Trabelsi AM. Total Neoadjuvant Therapy versus Neoadjuvant Chemoradiotherapy and Adjuvant Chemotherapy in Locally Advanced Rectal Cancer: Comparable Survival with Enhanced Tumor Response. Arch Int J Cancer Allied Sci. 2025;5(1):40-52. https://doi.org/10.51847/PXeXWf0Pa3

chemoradiotherapy and high-quality TME [9], though adherence to adjuvant therapy was suboptimal [9-11]. Such equivocal data on adjuvant chemotherapy benefits have led to varying clinical recommendations [12, 13].

Administering full systemic chemotherapy prior to chemoradiotherapy and operation—termed TNT—seeks to boost tumor downstaging, enhance treatment adherence, and address micrometastases promptly [14-18]. With rising emphasis on organ-sparing approaches for those attaining clinical complete response (cCR) after neoadjuvant regimens, tumor regression stands as a key endpoint [19–22]. Accumulating data support TNT's superior impact on regression compared to standard approaches [14-18], but its potential to improve survival over chemoradiotherapy with planned adjuvant therapy is debated [23]. Earlier, we described initial TNT implementation in LARC, noting enhanced regression with TNT relative to chemoRT [16]. Here, we present refreshed data on regression rates alongside analyses of DFS, local recurrence-free survival, distant metastasis-free survival, and overall survival. Additionally, we examine associations between regression status and DFS across the full cohort and by treatment category.

Materials and Methods

Patients

The cohort for this analysis included individuals diagnosed with locally advanced rectal cancer (LARC) at Memorial Sloan Kettering Cancer Center from June 1, 2009, to March 1, 2015, consistent with our earlier report [16]. Locally advanced disease was classified as stage II (T3-4, N0) or stage III (any T, N1-2) adenocarcinoma of the rectum located within 15 cm of the anal verge, following American Joint Committee on Cancer criteria. Staging of the locoregional area relied on endorectal ultrasound (ERUS) or magnetic resonance imaging (MRI). Exclusion criteria encompassed prior pelvic irradiation, hereditary polyposis conditions, inflammatory bowel disorders, recurrent rectal tumors, distant metastases, or additional malignancies diagnosed in the preceding 5 years. Among the participants, 311 underwent neoadjuvant chemoradiotherapy with planned subsequent adjuvant chemotherapy (chemoRT group), whereas 313 were managed with total neoadjuvant therapy (TNT), involving initial fluorouracil- and oxaliplatin-containing chemotherapy followed by chemoradiotherapy. Notably, 9 patients (out of 313) in the TNT arm also received chemotherapy after surgery. Institutional Review Board approval was obtained from Memorial Sloan Kettering Cancer Center.

Regimens

The chemoradiotherapy component delivered 25 to 28 fractions of 1.8 Gy, administered concurrently with continuous infusion fluorouracil at 225 mg/m² daily or oral capecitabine at 825 mg/m² twice daily. Radiation dosing typically involved 45 Gy to the pelvis, supplemented by a sequential or simultaneous boost of 5-11 Gy targeting the primary tumor. Individuals in the chemoRT arm were advised to complete adjuvant chemotherapy for an overall duration of 3 to 4 months, aligning with National Comprehensive Cancer Network recommendations [12]. For those in the TNT cohort, the regimen comprised approximately 4 months of upfront chemotherapy using either mFOLFOX6 (leucovorin, fluorouracil, oxaliplatin) or CAPOX (capecitabine plus oxaliplatin), with chemoradiotherapy initiated 2 to 3 weeks following completion of induction therapy [16].

Resection

Across both arms, patients achieving clinical complete response (cCR) upon finishing neoadjuvant treatment were offered participation in a watch-and-wait (WW) approach for organ preservation [19]. Those with cCR who opted for operation, individuals lacking cCR on reassessment, and cases experiencing tumor regrowth during WW proceeded to total mesorectal excision (TME). A subset avoided TME: local excision was performed in 4 patients (1%) from the TNT group and 1 patient (0.3%) from the chemoRT group; unresectability affected 2 patients (0.6%) in the TNT group; surgery was declined by 2 patients (0.8%) in the chemoRT group and 9 patients (3%) in the TNT group.

Outcomes

Complete response was characterized as pathologic complete response (no viable tumor cells identified in the resected specimen, as detailed previously [24, 25]) or sustained clinical complete response lasting 2 years (per established standards [21, 26, 27]). Assessment of clinical complete response incorporated endoscopic evidence of a flat white scar with unremarkable digital rectal examination, alongside pelvic MRI showing no suspicious residual tumor or lymphadenopathy. All survival endpoints were calculated from the initiation of neoadjuvant therapy. Events for local recurrence-free survival encompassed postoperative local recurrence,

unsalvageable regrowth in WW participants, or death. Distant metastasis-free survival considered distant metastases or death as events. Disease-free survival incorporated local recurrence post-TME, non-salvageable WW regrowth, distant metastases, or death. Overall survival was defined by death alone.

Statistical analysis

Comparisons of baseline patient and treatment features between groups employed the χ^2 test for categorical data and t-test or analysis of variance for continuous data. Survival distributions were assessed via the log-rank test. Given the retrospective design and potential for imbalances in prognostic factors (both measured and unmeasured), multivariable Cox proportional hazards models were constructed, incorporating variables selected from (1) univariable findings, (2) established prognostic indicators, and (3) factors differing between groups. Model fitting addressed collinearity, low-event categories, and proportionality assumptions. Variables with substantial missing data were omitted to preserve adequate sample size. An exploratory multivariable Cox analysis examined the interaction between neoadjuvant regimen and tumor response. Statistical significance was set at $P < 0.05$ for all tests. Analyses utilized SAS version 9.4 and R version 3.1.1 software.

Results and Discussion

Characteristics of chemort and tnt groups

Clinicopathologic and treatment characteristics for the chemoRT (n = 311) and TNT (n = 313) cohorts are presented in **Table 1**. Patients in the chemoRT group were older than those in the TNT group ($P < .001$). Most patients were male (chemoRT 60%, TNT 59%). TNT patients had higher proportions of cT4 tumors and node-positive disease. MRI was used for staging more frequently in TNT than in chemoRT patients (96% vs. 64%, $P < .001$). Median tumor distance from the anal verge did not differ significantly between the two groups.

Table 1. Patient and treatment characteristics

Characteristic	No. of patients (%)	P value[a]	Total Neoadjuvant Therapy (n = 313)	Chemoradiotherapy (n = 311)
Age[b,c]		<.001	55 ± 13 years	59 ± 13 years
Sex				
Female		.7	129 (41)	123 (40)
Male			184 (59)	188 (60)
Clinical T category		.007		
1 or 2			21 (6.7)	23 (7.4)
3			252 (81)	271 (87)
4			40 (13)	17 (5.5)
Clinical N status		<.001		
Negative			45 (14)	92 (30)
Positive			268 (86)	219 (70)
Method of locoregional staging		<.001		
MRI			287/299 (96)	151/236 (64)
ERUS			12/299 (4)	85/236 (36)
Tumor distance from anal verge[b,d]		.2	6.9 ± 3.0 cm	6.6 ± 2.9 cm
Radiation dose[b,e]		>.9	4,990 ± 344 cGy	4,991 ± 235 cGy
Chemotherapy not started		<.001	0/307	64/244 (26)
Total chemotherapy duration[b,f]		<.001	3.99 ± 0.53 mo	2.82 ± 2.00 mo
Pathological complete response[g]		.05	83 (27)	62 (20)

- One-way ANOVA or χ^2 test.
- Mean ± SD.
- Age (median, range): ChemoRT 58 (18–89) years; TNT 53 (22–89) years.

- Tumor distance from anal verge (median, range): ChemoRT 6.0 (0.0–15.0) cm; TNT 7.0 (0.0–15.0) cm. Missing: ChemoRT n = 30; TNT n = 36.
- Radiation dose (median, range): ChemoRT 5,040 (3,600–6,040) cGy; TNT 5,000 (2,500–8,060) cGy. Missing: ChemoRT n = 49; TNT n = 25.
- Total chemotherapy duration (median, range): ChemoRT 4.00 (0.00–9.00) months; TNT 4.00 (1.00–8.00) months.

Abbreviations: ERUS, endorectal ultrasound; CR, complete response; cCR, clinical complete response; TNT, total neoadjuvant therapy.

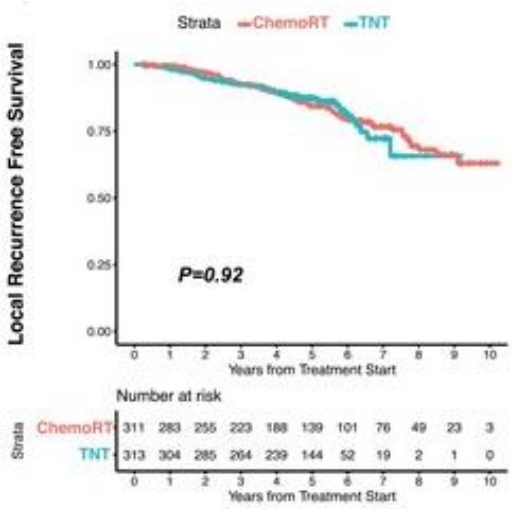
Mean radiation doses were similar between groups. All TNT patients initiated chemotherapy, whereas 26% of chemoRT patients did not receive postoperative chemotherapy (P < .001). The total chemotherapy duration was longer in TNT patients (3.99 vs. 2.82 months; P < .001).

Treatment response

Among chemoRT recipients, patients retaining a durable clinical complete response (cCR) declined from 19 (6%) one year after finishing neoadjuvant treatment to 14 (5%) at the two-year point. In the TNT cohort, those with ongoing cCR reduced from 70 (22%) at one year post-neoadjuvant completion to 39 (13%) at two years. At two years, the aggregate complete response rate (including pathologic CR or cCR) was greater in TNT than in chemoRT (27% vs. 20%; P = .05).

Survival outcomes

Follow-up medians were nearly identical: 4.9 years [range 0.24-10.4] in the chemoRT cohort and 5.0 years [range 0.86-9.2] in the TNT cohort, during which 154 disease-free survival events occurred (70 chemoRT, 84 TNT). Local recurrence-free and distant metastasis-free survival rates showed no substantial group differences (**Figures 1a and b**). Three-year disease-free survival reached 85% (81-90%; 95% CI) for chemoRT versus 79% (75-84%; 95% CI) for TNT, yet the Kaplan-Meier DFS curves did not differ significantly (P = .11; **Figure 1c).** Similarly, three-year overall survival was 94% in chemoRT and 96% in TNT (P = .25; **Figure 1d**).



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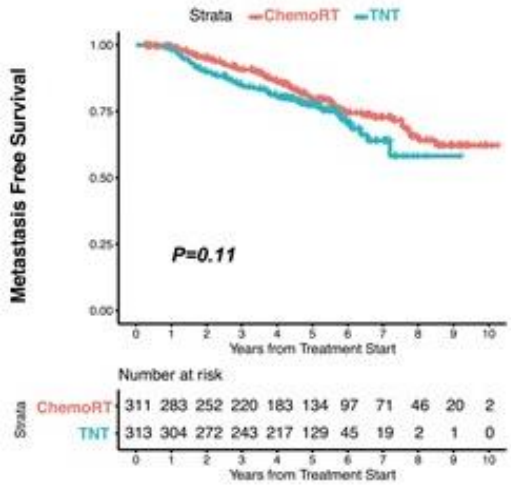

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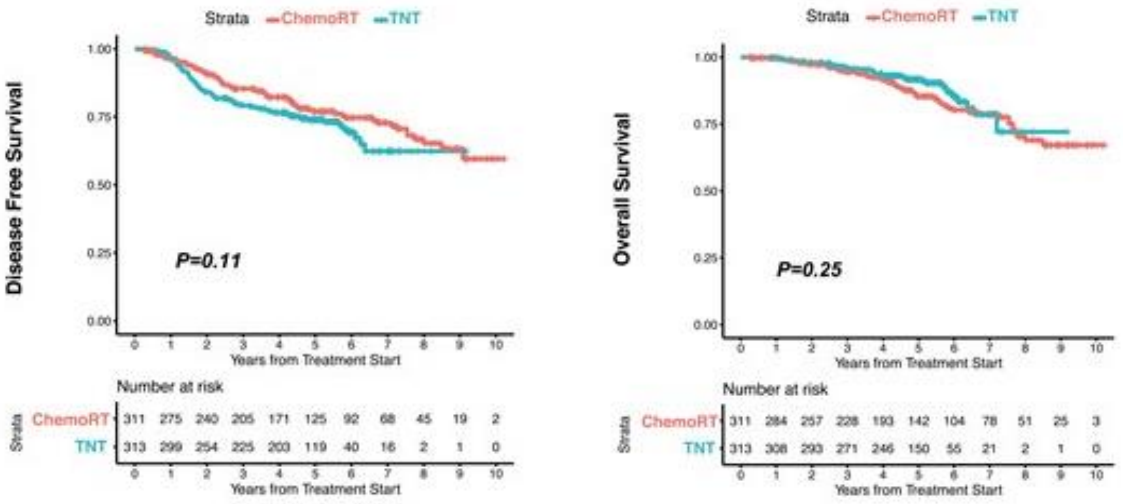


c) d)

Figure 1. Kaplan-Meier plots depicting survival metrics for the chemoradiotherapy (chemoRT) cohort and the total neoadjuvant therapy (TNT) cohort. Overall, 624 individuals underwent chemoRT (n=311) or TNT (n=313). Annual at-risk counts are indicated below the graphs. (a) Local recurrence-free survival. (b) Distant metastasis-free survival. (c) Disease-free survival. (d) Overall survival. Survival metrics showed no significant differences between chemoRT and TNT groups.

In single-variable assessment, disease-free survival correlated with clinical T4 stage (HR, 2.32; 95% CI 1.51-3.57; P<.001) and complete response (HR, 0.23; 95% CI 0.13-0.42; P<.001) **(Table 2).** Male gender also trended toward poorer disease-free survival (HR, 1.37; 95% CI 0.98-1.91; P=.066). Subsequently, multiple-variable regression was conducted, incorporating baseline clinical features that varied across cohorts or linked to disease-free survival in the single-variable phase **(Table 3).** Male gender (HR, 1.62; 95% CI 1.11-2.37; P=.012) and clinical T4 tumors (HR, 2.26; 95% CI 1.39-3.70; P=.001) exhibited notable ties to disease-free survival. Tumor response was further integrated into the multiple-variable framework **(Table 4),** revealing complete response (HR, 0.20; 95% CI 0.10-0.39; P<.001) alongside male gender and clinical T4 tumors as key predictors. No links were detected between disease-free survival and neoadjuvant regimen type, rectal tumor location, clinical nodal status, imaging modality for staging, or overall chemotherapy length.

Table 2. Univariable analysis of factors potentially influencing disease-free survival.

Characteristic	P value	Hazard Ratio (95% CI)
Age	.1	1.01 (1.00-1.02)
Sex		
Female		Reference
Male	.066	1.37 (0.98–1.91)
Clinical T category		
1 or 2	.2	0.6 (0.28–1.29)
3		Reference
4	<.001	2.32 (1.51-3.57)
Clinical N status		
Negative		Reference
Positive	.4	1.19 (0.81-1.77)
Locoregional staging method		
MRI	.087	1.54 (0.94-2.51)

ERUS		Reference
Tumor distance from anal verge	>.9	1 (0.94-1.06)
Neoadjuvant treatment		
ChemoRT		Reference
TNT	.11	1.3 (0.94-1.80)
Response		
Incomplete		Reference
Complete[a]	<.001	0.23 (0.13-0.42)
Total duration of chemotherapy[b]	.4	0.96 (0.86-1.07)

P-values were calculated using the Wald test. Complete response (CR) was defined as either a pathologic CR or a sustained clinical CR (cCR) maintained for 2 years. Chemotherapy duration reflects the combined months of neoadjuvant and adjuvant treatment.

Table 3. Multivariable analysis of clinial variables potentially affecting disease-free survival (DFS).

Characteristic	P value	Hazard Ratio (95% CI)
Age	.069	1.01 (1.00-1.03)
Gender		
Female		Reference
Male	.012	1.62 (1.11-2.37)
Clinical T category		
1 or 2	.5	0.74 (0.32-1.71)
3		Reference
4	.001	2.26 (1.39-3.70)
Clinical N status		
Negative		Reference
Positive	.4	1.19 (0.76-1.87)
Locoregional staging method		
ERUS		Reference
MRI	.3	1.30 (0.76-2.21)
Neoadjuvant treatment		
ChemoRT		Reference
TNT	.4	1.20 (0.80-1.78)

Sample size for this analysis was 535 patients, with a total of 132 events. P-values were determined using the Wald test.

Table 4. Multivariable analysis ofclinicopathological variables associated with disease-free survival (DFS).

Characteristic	Hazard Ratio (95% CI)	P value
Age	1.02 (1.00-1.03)	.021
Gender		
Female	Reference	
Male	1.59 (1.10-2.32)	.014
Clinical T category		
1 or 2	0.93 (0.41-2.15)	.9
3	Reference	
4	1.99 (1.22-3.24)	.006
Clinical N status		
Negative	Reference	
Positive	1.07 (0.68-1.67)	.8
Locoregional staging method		
ERUS	Reference	
MRI	1.26 (0.73-2.15)	.4

Neoadjuvant treatment		
ChemoRT	Reference	
TNT	1.31 (0.88-1.95)	.2
Response		
Incomplete	Reference	
Complete[a]	0.20 (0.10-0.39)	<.001

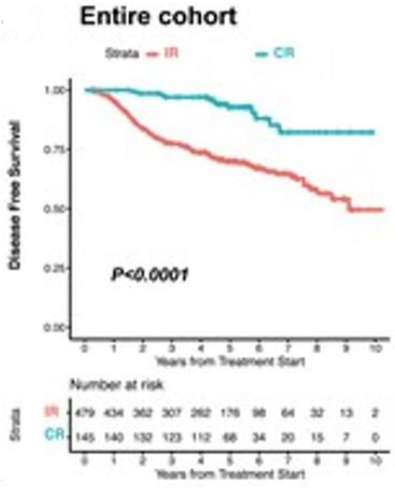
The cohort for this analysis consisted of 535 patients, with 132 recorded events for disease-free survival (DFS). Statistical significance was evaluated using the Wald test. Complete response (CR) was defined as either pathologic CR or clinical CR (cCR) maintained for a minimum of 2 years.

To explore in greater depth the connection between tumor regression and disease-free survival (DFS), we examined survival outcomes stratified by response category (complete response versus incomplete response) across the full patient population and within each neoadjuvant regimen separately **(Figure 2).** Complete responders demonstrated superior DFS relative to those with incomplete responses in the overall group (Wald and log-rank P < .0001) **(Table 2, Figure 2a)**, as well as within individual treatment cohorts (log-rank P = .016 for chemoRT and P < .0001 for TNT) (**Figures 2b and c).** Graphically, the survival disparity between complete and incomplete responders seemed more substantial in the TNT cohort than in the chemoRT cohort. For a more formal assessment, we incorporated an interaction term into a multivariable regression to determine if the impact of response on DFS varied by neoadjuvant approach. This interaction between treatment type and response **(Table 5)** proved statistically significant (P = .021) following adjustment for relevant clinical and patient characteristics, suggesting a greater divergence in DFS trajectories between complete and incomplete responders among those treated with TNT versus chemoRT.

Table 5. Multivariable Cox regression analysis of DFS including an interaction term between neoadjuvant therapy and tumor response.

Characteristic	Hazard Ratio (95% CI)	P value
Age	1.02 (1.00-1.03)	.024
Gender		
Female	Reference	
Male	1.58 (1.09-2.29)	.017
Clinical T category		
1 or 2	0.90 (0.39-2.08)	.8
3	Reference	
4	1.93 (1.18-3.15)	.009
Clinical N status		
Negative	Reference	
Positive	1.05 (0.67-1.65)	.8
Locoregional staging method		
ERUS	Reference	
MRI	1.26 (0.74-2.16)	.4
Neoadjuvant treatment		
ChemoRT	Reference	
TNT	1.48 (0.98-2.25)	.064
Response		
Incomplete	Reference	
Complete[a]	0.45 (0.20-0.99)	.048
Interaction term		
TNT × Complete Response	0.15 (0.03-0.75)	.021

The analysis included 535 patients, with 132 events recorded for disease-free survival (DFS). Statistical significance was determined using the Wald test. Complete response (CR) was defined as either a pathological CR or a clinical CR (cCR) maintained for at least 2 years.



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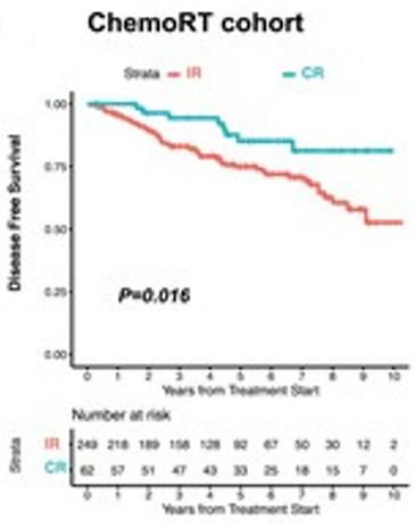

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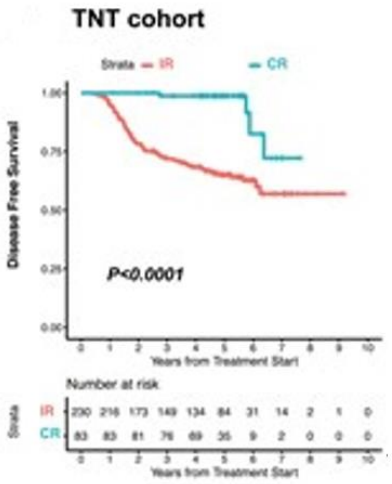

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Figure 2. Disease-free survival by response

Kaplan–Meier curves illustrating DFS according to tumor response (complete response [CR] vs. incomplete response [IR]) are presented. Panel A shows the full cohort (n = 624), Panel B displays the chemoRT group (n = 311), and Panel C shows the TNT group (n = 313).

This investigation reveals that, even with improved adherence to therapy and earlier administration of systemic agents, individuals with locally advanced rectal cancer (LARC) managed via total neoadjuvant therapy (TNT)—comprising upfront chemotherapy followed by chemoradiotherapy—do not achieve extended survival relative to those receiving chemoradiotherapy with planned postoperative chemotherapy. Although extended observation revealed tumor regrowth in certain watch-and-wait cases, the complete response rate remained superior in the TNT cohort versus the chemoradiotherapy group. Within our patient series, clinical T4 stage and complete response emerged as independent predictors of disease-free survival, aligning with prior publications [28]. The specific neoadjuvant strategy, however, showed no influence on survival endpoints, consistent with earlier studies reporting comparable long-term results between TNT and standard chemoradiotherapy [23, 29].

Non-comparative cohort studies indicated that upfront chemotherapy prior to chemoradiotherapy was generally well-accepted, offered prompt symptom control, and yielded strong tumor regression in LARC cases, though without direct survival comparisons to chemoradiotherapy alone [30-35]. One randomized

controlled study could not demonstrate enhanced regression with two cycles of induction mFOLFOX6 plus chemoradiotherapy versus chemoradiotherapy monotherapy in LARC, leading to premature closure [36]. The phase II GCR-3 trial, which assigned LARC patients to either TNT (four cycles of CAPOX then chemoradiotherapy) or standard sequencing (chemoradiotherapy followed by four cycles of CAPOX), observed equivalent regression and survival despite better chemotherapy completion in the TNT arm [29]. Notably, the trial lacked sufficient power for survival distinctions. In agreement with our findings, an analysis of National Cancer Database records for LARC patients demonstrated comparable survival between those receiving pre-chemoradiotherapy systemic therapy plus total mesorectal excision and a matched group undergoing chemoradiotherapy plus excision [23]. Similarly, the pre-chemoradiotherapy systemic group exhibited higher—though not significantly so—regression rates [23].

The RAPIDO trial recently reported reduced disease-related treatment failure among LARC patients given short-course radiotherapy followed by four months of FOLFOX or CAPOX, compared to chemoradiotherapy, excision, and discretionary adjuvant therapy. Yet, despite intensified chemotherapy in the investigational group, overall survival remained unchanged [37]. In the phase III PRODIGE-23 study, LARC patients were allocated to standard treatment (chemoradiotherapy, excision, and six months of adjuvant FOLFOX or CAPOX) or an intensified approach (three months of neoadjuvant mFOLFIRINOX, chemoradiotherapy, excision, and three months of adjuvant FOLFOX or CAPOX). The latter arm achieved greater regression, superior 3-year disease-free survival (75.7% vs. 68.5%; $P = .034$), and better 3-year metastasis-free survival (78.8% vs. 71.7%; $P < .02$) [38]. As the first to show disease-free survival gains with induction chemotherapy, this trial deviated from pure TNT by using a distinct agent (irinotecan) exclusively in the experimental group, suggesting outcomes may stem from drug addition rather than timing. Overall survival showed no difference despite escalation.

Our data affirm that complete responders to neoadjuvant regimens experience markedly better survival than incomplete responders [28]. One might expect higher complete response rates to elevate group-wide survival, but our results contradict this. The elevated complete response in TNT did not yield survival advantages over chemoradiotherapy. This mirrors multiple randomized trials revealing identical overall survival despite varying complete response rates across arms [10, 39-41]. Stratifying survival by response within each treatment arm offers insight into this disconnect: the wider divergence in disease-free survival curves between complete and incomplete responders in TNT versus chemoradiotherapy implies TNT selectively enriches complete responders from biologically indolent tumors while enriching poorer-prognosis cases among incomplete responders. These observations carry key implications, given complete response is often viewed as a proxy for survival in rectal cancer and serves as a trial endpoint.

Though toxicity data were not captured here, escalated chemotherapy dosing likely heightens adverse effects [42]. Since strong responders to chemoradiotherapy gain nothing from adjuvant therapy [5, 9], broad TNT adoption risks overtreatment in some LARC cases. Conversely, TNT's boosted response could expand organ-sparing eligibility. Early OPRA trial data indicate at least 40% of LARC patients receiving induction chemotherapy plus chemoradiotherapy may avoid resection if allowed adequate response time [43]. Thus, despite minimal survival impact, TNT merits priority for candidates favoring organ retention—particularly low-lying tumors risking anastomosis or permanent ostomy. Moreover, initiating with induction chemotherapy enables potential omission of radiotherapy (sparing related complications) in higher tumors amenable to sphincter-conserving excision [44, 45].

Limitations

This investigation carries multiple constraints stemming from its non-prospective nature. Over the study timeframe, neoadjuvant approaches for rectal cancer at our center underwent changes. Total neoadjuvant therapy was first implemented primarily for younger individuals presenting with higher-stage disease, potentially contributing to observed variations in age and clinical staging across cohorts. Moreover, staging modalities evolved, with early reliance on endorectal ultrasound giving way to magnetic resonance imaging in later periods. The superior visualization of the mesorectum and fascial planes afforded by MRI relative to ERUS might partly explain staging discrepancies between groups. Additionally, the rising incidence of rectal cancer in younger populations could underlie the age imbalances noted. A further drawback involves the growing

utilization of watch-and-wait strategies in recent times, evident in the larger fraction of such cases within the TNT cohort compared to the chemoRT cohort. Although watch-and-wait seems oncologically secure [43], the uneven distribution might have affected survival metrics. Whereas delivering chemoradiotherapy prior to systemic therapy in neoadjuvant sequencing has linked to enhanced regression [43], this work did not assess sequencing effects on survival endpoints. Despite efforts to control for confounders via multivariable modeling, residual selection bias or unidentified variables influencing outcomes cannot be ruled out.

Conclusion

The findings indicate that total neoadjuvant therapy elevates the probability of achieving complete response, potentially facilitating greater organ-sparing through watch-and-wait protocols, yet it yields no survival advantage over standard chemoradiotherapy succeeded by intended adjuvant chemotherapy.

Acknowledgments: We would like to thank Arthur Gelmis for editing the grammar of this manuscript.

Conflict of Interest: Rona Yaeger: Pfizer, Mirati Therapeutics, Natera RF: Pfizer, Boehringer Ingelheim (C/A); Neal H. Segal: Immunocore, PsiOxus, Roche/Genentech, Boehringer Ingelheim, Revitope, ABL Bio (C/A); Regeneron, Immunocore, AstraZeneca, BMS, Merck, Pfizer, Roche/Genentech (RF); Anna Varghese: OBI-Pharma, GSK Silenseed, Lilly, BMS (RF—inst); Abraham Yu: MORE Health (C/A); Civatech Oncology, Inc. (RF); Simphotek, Inc. (SAB); J. Joshua Smith: Guardant Health Inc. (C/A); Intuitive Surgical Inc. (Other—travel); Julio Garcia-Aguilar: Ethicon, Da Vinci Intuitive Surgical, Medtronic and Johnson and Johnson (H); Intuitive Surgical (OI); Zsofia Stadler: Alcon, Adverum, Gyroscope Therapeutics Limited, Neurogene, RegenexBio (C/A—family member); Paul B. Romesser: EMD Serono (C/A, RF); Elekta, Philips Healthcare (Other—travel). The other authors indicated no financial relationships.
(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent-holder; (SAB) Scientific advisory board.

Financial Support: The study was supported by National Institutes of Health (grant P30 CA008748). JKK was supported in part by NIH (grant T32CA009501).

Ethics Statement: None

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