

Disruptive Analysis of Total Neoadjuvant Therapy in Locally Advanced Rectal Cancer: Clinical and Therapeutic Distinctions Between Low- and Mid-Rectal Cancers

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ABSTRACT

Total neoadjuvant therapy (TNT) has become a cornerstone in the treatment of locally advanced rectal cancer, improving systemic control and increasing the potential for organ preservation. However, current trials and guidelines continue to treat rectal cancer as a homogeneous entity, overlooking the significant anatomic and therapeutic differences between mid- and low-rectal tumors. This uniform approach fails to reflect the impact of tumor location on both oncologic outcomes and functional consequences. Low-rectal cancers—defined as tumors located < 1 cm from the anal ring—pose distinct anatomic and functional challenges. These include more complex lymphatic drainage, higher risks of positive margins, and greater impact on continence. By contrast, mid-rectal tumors are generally more amenable to standard resection with preserved function and may benefit from treatment deintensification, particularly regarding radiotherapy. Drawing on data from over 80 studies and clinical trials, this review argues that mid- and low-rectal cancers should be considered distinct clinical entities requiring tailored treatment strategies. We examine evidence supporting radiotherapy de-escalation for mid-rectal tumors and intensified TNT for low-rectal tumors when organ and sphincter preservation is essential. Adopting a location-specific, patient-centered approach can better align treatment intensity with oncologic risk and individual functional priorities, ultimately improving both outcomes and quality of life.

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INTRODUCTION

The management of locally advanced rectal cancer (LARC) is constantly evolving. Standardization of total mesorectum excision (TME) technique by Heald et al¹ markedly reduced local recurrence and remains the surgical cornerstone. Delivering radiation before TME further improved local control for patients with high-risk tumors.^{2,3} Until recently, neoadjuvant treatment of LARC (T3-T4 and/or N+) relied on either short course radiotherapy (SCRT; 25 Gy in five fractions over 5 days) or long-course radiotherapy (45–50 Gy in five fractions per week) combined with concomitant 5-fluorouracil or capecitabine, followed by TME. The Dutch TME trial demonstrated that adding SCRT to TME significantly reduced local recurrence (2.4% v 8.2%),² an effect that persisted at 10-year follow-up.⁴ Subsequent trials confirmed the benefit of preoperative radiotherapy in reducing significantly local recurrence rates.^{5–8} Disappointingly, no improvement in overall survival (OS) was observed. The European Organisation for Research and Treatment of Cancer (EORTC) 22921 and Fondation Française de Cancérologie Digestive 9203 clinical trials demonstrated that

patients receiving preoperative chemoradiotherapy (CRT) had significantly decreased local recurrence rate compared with those treated with preoperative radiotherapy alone (8% v 17% respectively).^{9,10} However, no significant difference in OS was found.

Adjuvant chemotherapy after surgery remains widely used to mitigate the risk of metastatic recurrence, but randomized trials^{11–14} and meta-analysis¹⁵ have failed to demonstrate a significant benefit in terms of OS, disease-free survival (DFS), or distant recurrence. A major challenge in these studies has been the low compliance with adjuvant chemotherapy, with only 43% completing all cycles of chemotherapy in EORTC trial,¹³ 48% in the CHRONICLE trial,¹² and up to 73.6% in PROCTOR-SCRIPT trial.¹¹ This poor adherence to treatment may have influenced the results. However, the ADORE trial, which specifically evaluated the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy in ypStage II/III patients after neoadjuvant CRT, showed a significant improvement in DFS with the leucovorin, 5-FU and oxaliplatin (FOLFOX) regimen, particularly in poor responders (ypStage III patients).¹⁶

Beyond oncologic outcomes, radiotherapy (either short or long course) followed by TME significantly affects functional outcomes, including urinary, sexual, and bowel dysfunctions, leading to a reduced quality of life (QoL).¹⁷⁻¹⁹ Most patients experienced significant decline in urinary, erectile, and ejaculatory dysfunction among men after irradiation and even more after surgery. Similar trends have been observed in female sexual activity.²⁰ Moreover, the Dutch Colorectal Cancer Group reported higher rates of fecal incontinence and pad use, with a greater impact of bowel dysfunction on daily activities in irradiated patients compared with those who underwent TME alone.²¹ Similarly, Battersby et al²² found that 85% of patients experienced bowel-related QoL impairment, with 40% reporting major impairment.

These findings have led to increasing interest in organ preservation (OP) strategies for patients achieving a clinical complete response (cCR) after neoadjuvant therapy. Advances in total neoadjuvant therapy (TNT) have led to higher pathologic complete response (pCR) rates compared with CRT²³⁻²⁷ raising the question of whether rectal removal is necessary in such cases. Nonoperative management (NOM) has emerged as a viable alternative to surgery, with the watch and wait (W&W)²⁸ and selective local excision (LE)^{29,30} These strategies allow well-selected patients with a cCR to avoid surgery, thereby reducing sequelae, while achieving equivalent oncologic outcomes comparable with CRT followed by TME.²⁸⁻³²

Given these evolving paradigms, the concept of de-escalation of overall treatment has emerged raising whether surgery should be avoided in favor of an OP strategy or whether radiotherapy should be reconsidered because of its adverse functional outcomes. Randomized trials evaluating these approaches in LARC have primarily focused on mid- and low-rectal cancers, although eligibility criteria and tumor height definitions vary across studies. Low-rectal cancers are defined as tumors with a distal edge <1 cm from the anal ring and mid-rectal cancer as >1 cm from the anal ring to 8-10 cm from the anal verge. The distinction, on the basis of anatomy rather than molecular features, directly affects surgical decision making and therapeutic strategies. First, the risk profiles differ mainly in vascularization and lymphatic drainage, with important prognostic implications. Low-rectal cancers have complex vascular supply (superior, middle, and inferior rectal arteries) and dual lymphatic drainage, with potential spread to mesorectal, internal iliac, obturator, and even inguinal lymph nodes, making both oncologic and surgical management more challenging. Their proximity to the sphincter limits the ability to achieve wide surgical margins, often making curative resection more challenging compared with mid-rectal tumors. Second, treatment objectives after neoadjuvant treatment also vary by tumor location.³³ In mid-rectal cancers, sphincter preservation is generally not a major issue, as it can usually be achieved with standard surgery. Two main strategies are therefore debated in mid rectal cancer: OP approach, if

tumors are palpable on digital clinical examination to allow close surveillance or avoid radiotherapy to minimize long-term functional impairment after TME. By contrast, low-rectal cancers, particularly in very low-rectal cancers, that is, < 1 cm from the anal ring, prioritize organ and sphincter preservation.³⁴ However, even when preserved, sphincter function is often severely impaired, particularly especially after low colo-anal anastomosis or intersphincteric resection. This functional burden reinforces OP strategies whenever oncologically safe, underscoring the need for individualized, location-specific treatment strategies balancing oncologic safety with QoL outcomes.

The aim of this literature review was to summarize all randomized trials on the treatment of mid- and lower-rectal cancers and to propose the most appropriate strategy based on tumor location. This review focuses on proficient mismatch repair rectal cancers, as deficient mismatch repair/microsatellite instability-high tumors demonstrate exceptional sensitivity to PD-1 blockade, requiring a distinct therapeutic approach.^{35,36} High-rectal cancers involve different surgical and oncologic considerations and are therefore outside the scope of this review.

TOTAL NEOADJUVANT THERAPY

TNT has emerged as an alternative to SCRT alone or long-course CRT, addressing the challenges of poor compliance with adjuvant chemotherapy.³⁷ By delivering preoperatively full-dose chemotherapy (in combination with SCRT or CRT), TNT can be administered as either induction chemotherapy INCT-CRT (before radiotherapy) or consolidation chemotherapy CRT-CNCT (after radiotherapy). The randomized clinical trials referenced below are summarized in [Table 1](#).

Short-Course Radiotherapy

Randomized trials^{38,39} demonstrated no significant difference in 5-year oncologic outcomes between SCRT followed by immediate surgery and CRT with delayed surgery in resectable rectal cancer. However, Bujko et al reported higher early toxicity in the CRT group (18.2% v 3.2%, $P < .001$). Based on these findings, the POLISH II trial was one of the first randomized trials to investigate TNT, suggesting that SCRT-CNCT might thereby be superior to CRT.⁴⁰ Patients with cT3/cT4 rectal cancer or locally recurrent were allocated to either preoperative TNT (SCRT followed by three cycles of FOLFOX) or conventional CRT. Among 515 patients, R0 resection rate (primary end point) did not significantly differ between groups. Although local failure (22% v 21%), distant metastasis (DM) (30% v 27%) and pCR rates (16% v 12%) were similar, TNT improved 3-year OS without long-term survival benefit.⁴¹ The STELLAR noninferiority trial involved 599 patients with cT3-4 middle/low-rectal cancer and/or N + M0 and randomized either SCRT followed by four cycles of chemotherapy (CAPOX) or CRT.²⁵ Although the 3-year DFS rate and metastasis-free survival (MFS) rates were similar

TABLE 1. Randomized Trials of Total Neoadjuvant Therapy in Patients With Advanced Rectal Cancer

Study	Inclusion Criteria	No.	Study Design	Primary End Point	R0 Rate (%)	pCR Rate (%)	OS (%)	DFS (%)	Adjuvant CT (%)
Randomized trials with SCRT									
POLISH II	cT3-4 or recurrent rectal cancer	515	SCRT + 3 cycles of FOLFOX4 v CRT	R0 rate	77 71	16 12	3-year: 73 v 65 ^a 8-year: 49	3-year: 53 v 52 8-year: 43 v 41	39 in both groups
STELLAR	cT3-4 and/or N+ (mid/distal rectal cancer)	599	SCRT + 4 cycles of CAPOX v CRT	DFS	91.5 87.8	21.8 ^a 12.3	86.5 ^a 75.1	64.5 ^a 62.3	TNT: 77 CRT: 73.9
RAPIDO	cT4a-b; cN2; EMVI; MRF+ (<16 cm AV)	920	SCRT + 6 cycles of CAPOX or 9 cycles of FOLFOX v CRT	Disease-related treatment failure	90	28 ^a 14	5-year: 81.7 v 80.2	3-year: 23.7 v 30.4 ^a 5-year: 27.8 v 34 ^a	CRT: 41.6
Randomized trials with long-CRT									
CAO/ARO/AIO-12	Stage II/III (<12 cm AV)	306	INCT-CRT v CRT-CNCT	pCR	92 90	17 25	5-year: 85.7 v 84.2	3-year: 73	—
OPRA	Stage II (distal, <6.5 cm AV)	324	INCT-CRT v CRT-CNCT	DFS	91 88	NS	5-year: 88 v 85	3-year: 76 5 year: 71 v 69	—
PRODIGE 23	cT3-4 (≤12 cm AV)	461	INCT-CRT v CRT	DFS	95 94	28 ^a 12	5-y: 86.9 v 80 ^a 7-y: 81.9 v 76.1 ^a	3-year: 76 v 69 ^a 7-year: 67.6 v 62.5 ^a	TNT: 77 CRT: 79

Abbreviations: AV, anal verge; CRT, course radiotherapy; CRT-CNCT, CRT followed by consolidation chemotherapy; CT, chemotherapy; DFS, disease-free survival; EMVI, extramural venous invasion; FOLFOX, leucovorin, 5-FU and oxaliplatin; INCT-CRT, induction chemotherapy followed by CRT; MRF, mesorectal fascia; NS, not specified; OS, overall survival; pCR, pathologic complete response; SCRT, short-course radiotherapy.

^aSignificant difference.

between groups, TNT resulted in a significantly higher pCR rate (21.8% v 12.3%, $P = .002$) and superior 3-year OS rate (86.5% v 75.1%, $P = .03$) but with a higher acute grade toxicity $\geq$ III (26.5% v 12.6%, $P < .001$). Based on the previous Dutch trial,⁴² the RAPIDO trial included 912 patients with LARC with distal extension <16 cm from the anal verge.²⁴ Unlike previous studies, the RAPIDO trial included only high-risk patients, each fulfilling at least one of the subsequent criteria: cT4a-b, extramural vascular invasion, cN2, or mesorectal fascia involvement. Participants were randomly assigned to SCRT followed by six cycles of CAPOX/nine cycles of FOLFOX or CRT. Disease-related treatment failure rate, a protocol specific end point, was significantly reduced in the TNT arm at 3 years ($P = .019$), but not at 5 years ($P = .048$), the final analysis being planned at a nominal alpha level of 0.0424.⁴³ The lower rate in the experimental group was primarily driven by a statistically decreased rate of DM at 5 years (23% v 30.4%, $P = .011$). It is important to note that while 100% of patients in the experimental arm received consolidation chemotherapy, only 41.6% of patients in the control group received adjuvant chemotherapy, which may have contributed to the better systemic control observed in the experimental arm, leading to fewer DM. Two other results should be highlighted: Higher pCR (28.4% v 14.3%) but higher locoregional recurrence after R0/R1 resection (10% v 6%, $P = .03$) were found in the TNT group.⁴³ Moreover, a longer interval between radiotherapy and surgery in the experimental arm than the CRT arm may have resulted in more downstaging and possibly a higher proportion of pCR. By contrast, for patients who had poor response to therapy, the longer interval between random assignment and surgery in the experimental arm may have been detrimental, as demonstrated by the higher number of residual pathologic T4 (ypT4) tumors (9% v 6%), a lower rate of intact mesorectum (78% v 85%, $P = .032$),⁴⁴ and the higher local recurrence rate in the experimental arm. In the GRECCAR6 trial, a poorer quality of mesorectal resection was observed in the experimental group (surgery at 11 weeks after TNT) compared with the standard group (7 weeks).⁴⁵ Furthermore, the RAPIDO trial demonstrated a significant reduction of DM rate without OS benefit, potentially reflecting the ATRESS phenomenon (neoAdjuvant Therapy-Related Shortening of Survival). ATRESS is a proposed hypothesis suggesting that although intensified neoadjuvant treatment may prevent the occurrence of metastases, it could also negatively affect survival once metastases have developed.⁴⁶ In the RAPIDO trial, median survival after DM was 6 months longer in the standard-of-care group than in the TNT group. Patients who develop DM after such intensified neoadjuvant therapy might experience more aggressive disease progression or reduced tolerance to further systemic treatment, ultimately shortening postmetastatic survival. The RAPIDO study emphasizes the importance of the balance between systemic control and local control. Although SCRT-CNCT prevents DM, the higher rate of local recurrence highlights the need for first an appropriate combination of radiotherapy and chemotherapy, especially in high-risk patients, and second an assessment of tumor response after each step of treatment.

Long-Course Radiotherapy

The German phase II trial CAO/ARO/AIO-12 was the first to compare INCT-CRT to CRT-CNCT.²⁶ Among 306 patients with stage II/III rectal cancer, preoperative radiotherapy consisted of 50.4 Gy while induction/consolidation chemotherapy included three cycles of FOLFOX. CRT-CNCT, followed by TME improved pCR rates (defined as ypT0N0) of 25% versus 17% in INCT-CRT without significant differences in 3-year DFS, DM, or cumulative local recurrence.⁴⁷ Five-year OS was comparable in both arms (85.8% v 84.2%), regardless of whether patients received INCT-CRT or CRT-CNCT.⁴⁸

Similarly, the OPRA phase II trial compared INCT-CRT and CRT-CNCT in patients with stage cT3-4N0 or cTxN1-2 rectal cancer with DFS at its main objective.³² Among patients restaged at the end of TNT, 74% were eligible for the W&W protocol. Although 5-year DFS rates were similar, the OPRA trial found that CRT-CNCT achieved superior 5-year TME-free survival compared with the INCT-CRT arm (54% v 39%, $P = .012$), supporting its role in OP strategies. The higher OP rate in patients treated with CRT-CNCT compared with INCT-CRT aligns with the findings of the CAO/ARO/AIO-12 trial. One possible explanation for this high response is the longer interval between the end of CRT and surgery in CAO/ARO/AIO-12 or restaging in the OPRA study (45 and 90 days for the induction and consolidation group in CAO/ARO/AIO-12 trial, respectively, and 8 weeks and 28.5 weeks for the induction and consolidation group in OPRA trial, respectively). However, in OPRA trial, actual cCR rates were similar between the two arms (51% and 58%, respectively), suggesting either that the role of the time elapsed is less likely to be responsible for the difference in OP rates or that the role of the time is to improve the accuracy of the tumor response assessment. Indeed, this second option might be supported by the fact that, despite the similar cCR rate, INCT-CRT, in which restaging was earlier, resulted in higher rates of local regrowth (44% v 29%) among patients initially managed with W&W. Although long-term oncologic results are similar, both studies suggest that CRT-CNCT should be the preferred TNT sequence if OP is the primary goal. More recently, a higher rate of pCR in LE specimen has been reported in GRECCAR 12 trial comparing TNT with INCT-CRT to CRT with OP rate as primary outcome (Denost, manuscript in preparation).⁴⁹

The French PRODIGE 23 trial was the first phase III trial to evaluate induction triplet chemotherapy within a TNT strategy.²³ Patients with cT3-4, N0-2M0 rectal adenocarcinoma (<12 cm from the anal verge) were randomly assigned to either induction chemotherapy (six cycles of leucovorin, 5-FU, irinotecan and oxaliplatin [FOLFIRINOX]) followed by CRT versus CRT alone, both followed by TME and protocolized adjuvant chemotherapy. Administering neoadjuvant chemotherapy before CRT significantly improved both 5-year DFS (73.1% v 65.5%, $P = .02$) and long-term 7-year OS (81.9% v 76.1%, $P = .03$) compared with standard

CRT.⁵⁰ ATRESS phenomena did not occur and no difference in median survival after DM was observed between the TNT group and the standard-of-care group ($P = .71$). These results also reinforce that delivering systemic chemotherapy before CRT allows treatment of micrometastatic disease earlier, thereby reducing the risk of DM and contributing to improved long-term survival outcomes in LARC. Considering the encouraging results from triplet chemotherapy in PRODIGE 23, and the higher OP rates achieved with CRT-CNCT using doublet chemotherapy in the OPRA and CAO/ARO/AIO-12 trials, the debate surrounding the optimal TNT regimen remains ongoing. The Janus Rectal Cancer Trial is another phase III study that aims to compare neoadjuvant CRT followed by consolidation doublet (mFOLFOX6 or CAPOX) or triplet chemotherapy (mFOLFIRINOX).⁵¹ The primary endpoints are cCR and DFS for phase II and III, respectively. In parallel, the CCHOWW trial is an ongoing phase II study investigating whether adding oxaliplatin to consolidation chemotherapy following chemoradiation improves cCR rates and OP, further informing the role of triplet or doublet consolidation regimens in a W&W strategy.⁵²

TOWARD DE-ESCALATION: NONRADIOTHERAPY MANAGEMENT

Recent studies have explored the potential for de-escalation with a nonradiotherapy management (NRM) after neoadjuvant chemotherapy, with promising results with pCR rate of up to 33.3%⁵³ and tumor downstaging rates of up to 48%,⁵⁴ suggesting that some good responders may be overtreated with radiotherapy.⁵⁵ This approach aims to reduce urinary, sexual, and bowel dysfunction from pelvic radiotherapy, while maintaining oncological outcomes.

The Chinese FOWARC phase III trial was a randomized trial to compare neoadjuvant mFOLFOX6 chemotherapy alone, CRT, and CRT with mFOLFOX6 in patients with stage II-III rectal adenocarcinoma <12 cm from the anal verge, using 3-year DFS as the primary end point.⁵⁶ Although pCR rates were significantly lower with mFOLFOX6 alone (6.6% v 14% and 27.5%), tumor downstaging and R0 resection rates were comparable, and 3-year DFS, local recurrence rate, and OS were similar across groups⁵⁷ with similar results at 10 years.⁵⁸ However, the trial had a considerable number of patients lost to follow-up, which may limit the interpretability of the long-term outcomes. Additionally, the study was not adequately powered to detect meaningful differences in 3-year DFS between the arms, as it was only powered to detect a change from 60% to 75%. However, the sample size calculation for each group (165 patients) was sufficient to provide definitive conclusions regarding the efficacy of mFOLFOX6 alone versus CRT or CRT with mFOLFOX6. Although the results of the FOWARC trial provide valuable insights, the limited power and potential biases should be considered when interpreting the findings (Table 2).

The PROSPECT trial was a randomized trial comparing neoadjuvant FOLFOX with selective use of CRT to the

standard CRT.⁵⁹ This trial recruited 1,194 patients with intermediate-risk rectal cancer (cT2N1-2 or c T3N0-2), predominantly mid rectal cancer. High-risk T4 patients included in the FOWARC trial were excluded. Patients in the FOLFOX arm were restaged before surgery and CRT was administered to those with <20% tumor shrinkage ascertained based on a restaging magnetic resonance imaging (MRI) or those who were unable to complete at least five FOLFOX cycles. PROSPECT was an adequately powered trial and demonstrated no significant difference between FOLFOX alone and CRT in 5-year DFS (80.8% v 78.6%), 5-year OS (89.5% v 90.2%), and 5-year local recurrence rate (1.8% v 1.6%). However, pCR was slightly higher in CRT (24.3% v 21.9%) with no difference in the rates of R0 resection although this was likely attributable to the shorter interval between chemotherapy and surgery in the neoadjuvant FOLFOX group.

The NEO trial, a smaller study with 60 patients, explored a more targeted approach to OP in early-stage rectal cancer. The study aimed to evaluate the feasibility of avoiding TME by using neoadjuvant chemotherapy followed by transanal excision surgery. All patients with T1-T3abN0 low- and mid-rectal cancers received neoadjuvant FOLFOX chemotherapy, and those with suitable tumor characteristics underwent transanal excision. This trial demonstrated that neoadjuvant chemotherapy followed by transanal excision surgery could successfully downstage early-stage rectal cancer, achieving an OP rate of 57%. When including patients declining surgery, 79% avoided TME, with promising oncologic results. The 1-year and 2-year locoregional relapse-free survival was 98% and 90%, respectively, with no distant recurrences. However, the sample size was relatively small, and additional studies with larger cohorts are needed to confirm these findings and better assess the long-term durability of these outcomes.⁶⁰

In contrast to these studies, the CONVERT trial initiated in 2014, focused on high-risk patients with a majority of cT3-T4a (more than 80%) and N+ (almost 70% of patients) rectal cancer within 5-12 cm from the anal verge, all with clear mesorectal fascia (MRF) and evaluated the noninferiority of neoadjuvant CAPOX compared with CRT, using 3-year locoregional failure-free survival as the primary end point.⁶¹ It should be noted that from 2019, protocol was revised to enroll patients with low-rectal tumors (<5 cm from the anal verge). If disease progression was observed after chemotherapy alone, CRT was administered. No significant differences were found regarding in the primary end point or in R0 resection rates. Although pCR was similar, patients achieving tumor regression grade 0 to 1 were higher in the CRT group (36.8% v 23.2%, $P < .001$), likely because of differences in the interval between completion of treatment and surgical resection.

MRI has emerged as a key tool in assessing local tumor involvement, particularly circumferential resection margins (CRM), and in evaluating tumor response to neoadjuvant

TABLE 2. Randomized Trials of Neoadjuvant Chemotherapy Alone in Patients With Low Advanced Rectal Cancer

Randomized Trials Including a Neoadjuvant Chemotherapy Alone Group in Patients With Rectal Cancer									
Study	Inclusion Criteria	No.	Study Design	Primary End Point	R0 Rate (%)	pCR Rate (%)	5-Year OS (%)	DFS (%)	Adjuvant CT (%)
FOWARC	Stage II/III (<12 cm AV)	495	CRT mFOLFOX6 + RT mFOLFOX6	DFS	90.7 89.9 89.4	14 27.5 6.6	82.5 81.8 81.8	5-year: 65.2 v 67.7 v 67.5	70.3 v 81.2 v 85.4
PROSPECT	cT2N+ or cT3	1,194	mFOLFOX6 v CRT	DFS	90.4 91.2	21.9 24.3	89.5 v 90.2	5-year: 80.8 v 78.6	74.9 v 77.9
CONVERT	cT2N+, cT3-4 with clear MRF	663	CAPOX4 v CRT	3-year locoregional failure-free survival	99.6	11 13.8	95 v 94.1	3-year: 89.2 v 87.9	86.4 v 85
GRECCAR 4	T3 ≥c, T4 tumors, CRM ≤1 mm and tumors ≥1 cm from AV	206	FOLFIRINOX 4+ Good responders: TME v CRT (50 Gy) Bad responders: CRT (50 Gy) v CRT (60 Gy)	R0	100 v 100 82.7 v 87.8	10 v 57.9 15.4 v 24.4	5-year 90 v 93.3 84.3 v 86.1	5-year 80 v 89.5 72.9 v 72.8	—
NEOtrial	T1-T3abN0	58	m FOLFOX6/CAPOX	OP rate		57			—

Abbreviations: AV, anal verge; CRM, circumferential resection margins; CRT, chemoradiotherapy; CT, chemotherapy; DFS, disease-free survival; FOLFIRINOX, leucovorin, 5-FU, irinotecan and oxaliplatin; MRF, mesorectal fascia; NS, not specified; OP, organ preservation; OS, overall survival; pCR, pathologic complete response.

therapy. The MERCURY group demonstrated that MRI reliably predicts whether CRM will be clear or involved after TME.⁶² Moreover, baseline MRI-based CRM assessment outperforms TNM staging in predicting both local and distant recurrence, highlighting its value in risk-based patient stratification for neoadjuvant treatment.⁶³ By identifying tumors with a favorable prognosis preoperatively, the QUICKSILVER study further support the role of MRI as a reliable tool to select patient and optimization of preoperative therapy.^{64,65} The GRECCAR4 trial was the first published study to randomly assign patients with T3 $\geq$ c or T4 tumors and predictive CRM $\leq$ 1 mm, on the basis of MRI-assessed response after induction chemotherapy.⁶⁶ Good responders after four cycles of FOLFIRINOX ($\geq$ 75% tumor volume reduction with CRM $>$ 1 mm) were randomly assigned to either immediate surgery or CRT, while bad responders were randomly assigned to CRT or intensified CRT (CAP 60). Long-term follow-up of GRECCAR4 confirmed that avoiding radiotherapy in good responders did not compromise local control with similar R0 resection rates, whereas intensification in poor responders did not improve outcomes.⁶⁷ However, the GRECCAR4 trial had limitations, notably the small number of patients randomly assigned in good responders, possibly because of the high tumor response threshold required to omit radiotherapy, 75% of tumor volume shrinkage, versus 20% in PROSPECT trial.⁵⁹ To address this, the ongoing GRECCAR14 noninferiority trial evaluates early tumor response in patients with mid- or low-LARC with a predictive CRM $\leq$ 2 mm or T3c-d stage with extramural venous invasion or T4a-b (except bone and sphincteric invasion) after six cycles of FOLFIRINOX, defining good responders by a 60% tumor volume reduction on MRI.⁶⁸ The primary end point will be R0 resection for phase II and the 3-year DFS for phase III. A similar approach is being used in the ongoing NORAD01/GRECCAR16 trial, which randomly assigns patients with mid- or low-resectable LARC (cT3N0 or cT1-T3N+ with CRM $>$ 2 mm) to either modified FOLFIRINOX for 3 months or FOLFIRINOX followed by CRT.⁶⁹ The primary end point is 3-year progression-free survival (PFS). Although previous de-escalation studies compared chemotherapy alone with CRT at a time when TNT was not yet established as standard, the subsequent GRECCAR 14 and 16 trials were specifically designed to re-examine this question in the TNT era.

TOWARD DE-ESCALATION: NONOPERATIVE MANAGEMENT

Two main strategies have emerged in NOM: the opportunist approach with W&W strategy versus selective approach with LE. A key factor in these developments has been the increased pCR rate achieved with TNT, raising the question of whether surgery is necessary in certain patients. To our knowledge, Habr-Gama et al²⁸ were the first to describe the W&W strategy for LARC, relying on cCR assessment through clinical examination, MRI, and rectoscopy. Initial studies demonstrated equivalent long-term oncologic outcomes between patients who achieved cCR and were offered the W&W approach and those who underwent the traditional

TME surgery and were found to have a pCR in the surgical specimen, after CRT.^{28,31} Since then, several studies have evaluated the feasibility and outcomes of W&W approach after neoadjuvant treatment.^{70,71} However, recent studies have highlighted potential risks, particularly patients offered W&W who later develop tumor regrowth have a higher rate of DM compared with patients who had TME or LE and were found to have near complete pathologic response ($<$ 10% residual cancer cells) in the surgical specimen.^{72,73} However, initial tumor stage was more advanced in patients with surgery at regrowth. As highlighted in the correspondence by Garcia-Aguilar et al,⁷⁴ the control groups used in many studies may be inadequate and heterogeneous.

Alternatively, selective LE offers a minimally invasive surgical option for patients with nCR or cCR after neoadjuvant therapy. The ACOSOG trial demonstrated that LE following neoadjuvant CRT for cT2N0 rectal cancer ($<$ 4 cm) achieved favorable oncologic outcomes with only a 4% risk of local regrowth.²⁹ Similarly, the GRECCAR2 study analyzed patients with cT2-T3 rectal cancer ($<$ 4 cm) with good response to CRT (residual tumor $\leq$ 2 cm) and randomly assigned to either LE or TME. Among 148 patients included, nearly 60% had OP without compromising oncologic outcomes as local regrowth and metastasis rates were comparable with those observed in TME.³⁰ Additionally, LE is associated with significantly better functional outcomes, including lower rates of low anterior resection syndrome (LARS), compared with completion TME (5% v 47%, $P < .001$).⁷⁵ These findings support the selective approach of LE in good responders, achieving OP with functional advantages while maintaining long-term oncologic safety. Alternative strategies have been explored to further increase OP rates. The OPERA trial evaluated contact X-ray brachytherapy (CXB) combined with CRT in patients with cT2-T3bN0-1 rectal cancer, showing a 3-year OP rate of 81% versus 59% in external beam radiotherapy group, particularly for patients with tumors smaller than 3 cm.⁷⁶ This difference is still highly significant at 5 years.⁷⁷ Ongoing studies continue to refine OP strategies. For example, the STAR-TREC trial is evaluating OP strategies in cT1-3N0 rectal cancers $\leq$ 4 cm. Following neoadjuvant treatment, patients achieving a cCR may undergo a W&W strategy, whereas those with a near-complete response may be offered LE. This trial is expected to clarify whether a continuum exists between W&W and LE in the context of OP.⁷⁸

NOM offers clear advantages by preserving bowel function, a key determinant of postoperative QoL after TME. In the W&W setting, the median LARS score is 16 (no LARS), with 15% of patients experiencing major LARS.⁷⁹ Among those treated with LE, severe LARS occurs in about 5% of patients, compared with 47% after completion TME ($P < .001$).⁷⁵ However, these benefits must be balanced against potential drawbacks, including long-term neuropathy associated with intensive neoadjuvant treatment, the burden of intensive surveillance with related anxiety, and the risk of local regrowth sometimes requiring more extensive salvage

surgery. The risk of neuropathy mainly depends on chemotherapy duration and cumulative oxaliplatin exposure. In PRODIGE 23, grade ≥ 3 neuropathy occurred in 12% of patients in the TNT arm versus 21% in the standard arm, likely reflecting the longer interval between neoadjuvant mFOLFIRINOX and postoperative chemotherapy allowing partial neurological recovery.²³ Conversely, a recent meta-analysis⁸⁰ reported slightly higher neuropathy rates with TNT compared with standard CRT, probably because of greater cumulative exposure to oxaliplatin. Local regrowth occurs in 10%–25% of W&W patients^{70,71} often requiring more extensive salvage surgery that may compromise sphincter preservation. Finally, close surveillance may induce anxiety or fear of regrowth, as shown by Pennings et al⁸¹ who developed the Watch-and-Wait Patient-Reported Outcome Measure (WW-PROM) assessing emotional well-being, anxiety, and nervousness around follow-up visits.

TOWARD TAILORED MANAGEMENT BASED ON TUMOR LOCATION

Most studies regarding TNT have included rectal cancers located <12 cm from the anal verge without distinguishing between mid- and low-rectal tumors as different entities for random assignment of neoadjuvant treatment. This distinction is crucial, as treatment challenges and strategies vary significantly depending on tumor location.

Low-Rectal Cancers

Rullier et al³⁴ proposed a new classification, defining low-rectal cancer as tumors located <1 cm from the anal ring. The anal sphincter extends from the anal verge to the top of the anal canal (also known as anal ring or anorectal junction). Unlike traditional classifications, the new surgical classification defines the distal tumor boundary relative to the anal sphincter rather than the anal verge based on MRI imaging.⁸² This approach mitigates confusion caused by variations of the length of the anal sphincter (from 2 to 6 cm) and enables precise tumor localization, which is essential for tailoring surgical management.

Low-rectal cancers pose distinct challenges due to their proximity to the anal sphincters. Historically, abdominoperineal resection (APR) with a permanent colostomy was the standard approach. However, advances in neoadjuvant treatment—where radiotherapy was considered mandatory—and standardizing surgical techniques based on the new surgical classification have significantly improved sphincter preservation rates.^{83–86} However, these sphincter-sparing procedures are associated with functional disorders.^{87–89} These findings have driven the development of new strategies prioritizing OP. Patients with low-rectal cancer are probably the best candidates for OP strategies, including a combination of different neoadjuvant options such as TNT, CRT, or systemic chemotherapy, along

with consideration of baseline tumor stage and response to treatment.

For patients achieving cCR after TNT, a W&W strategy can be without compromising oncologic safety and functional outcomes. Additionally, for rectal tumors <1 cm from the anal ring, achieving a cCR is essential for proposing a NOM strategy, as LE and endocavitary radiotherapy are more challenging options for technical reasons.

Mid-Rectal Cancers

Mid-rectal cancers are located 5 to 10 cm from the anal verge or 1 to 7 cm from the upper part of anal canal.⁹⁰ The accuracy of distance assessment and the ease of reconstruction largely depend on the surgeon's experience, level of specialization, and commitment to the surgical management of rectal cancer. Unlike low-rectal cancers, mid-rectal cancers do not pose a significant challenge in terms of sphincter preservation when surgery is required. Instead, two key strategies should be considered: NRM to minimize long-term functional outcomes and NOM, particularly as mid-rectal tumors if tumors are palpable at digital examination, facilitating tumor response surveillance.

Recent studies such as GRECCAR4⁶⁶ and GRECCAR14⁶⁸ trials have demonstrated that using MRI-defined tumor response criteria after chemotherapy can effectively stratify patients for tailored treatment approaches. For good responders, radiotherapy could be omitted without compromising oncological outcomes.^{58,59,61} Moreover, in the era of TNT, ongoing NORAD-GRECCAR16 study, will confirm if omitting radiotherapy in patients with mid-rectal cancer with a free CRM does not compromise long-term oncologic results.⁶⁹ Moreover, avoiding radiotherapy prevents long-term toxicities such as sexual, digestive, and urinary complications. The PROSPECT trial demonstrated that QoL outcomes and symptom burden either favored or were superior with neoadjuvant FOLFOX compared with standard chemoradiation. Other potential advantages of avoiding CRT include decreased marrow toxicity, decreased risk of pelvic fractures, and decreased time and financial toxicity.⁵⁹ The CONVERT trial demonstrated a significantly lower rate of preventive ileostomy in the chemotherapy-alone group compared with standard CRT (52.2% v 63.6%, $P = .008$).⁶¹ On the other hand, a subset of patients with stage II/III mid-rectal cancer may safely avoid neoadjuvant CRT, instead undergoing up-front TME, with adjuvant chemotherapy offered selectively based on pathologic risk. This straight-to-surgery approach can reduce treatment-related toxicity and preserve function, particularly when sphincter preservation is not an issue. The OCUm trial supports this strategy, showing low local recurrence rates (1.3% at 3 years; 2.7% at 5 years) and acceptable DM rates (8.9% at 3 years; and 14.4 at 5 years) when patients were selected using MRI criteria, especially mesorectal fascia involvement.⁹¹

Therapeutic Distinctions Between Low- and Mid-Rectal Cancers

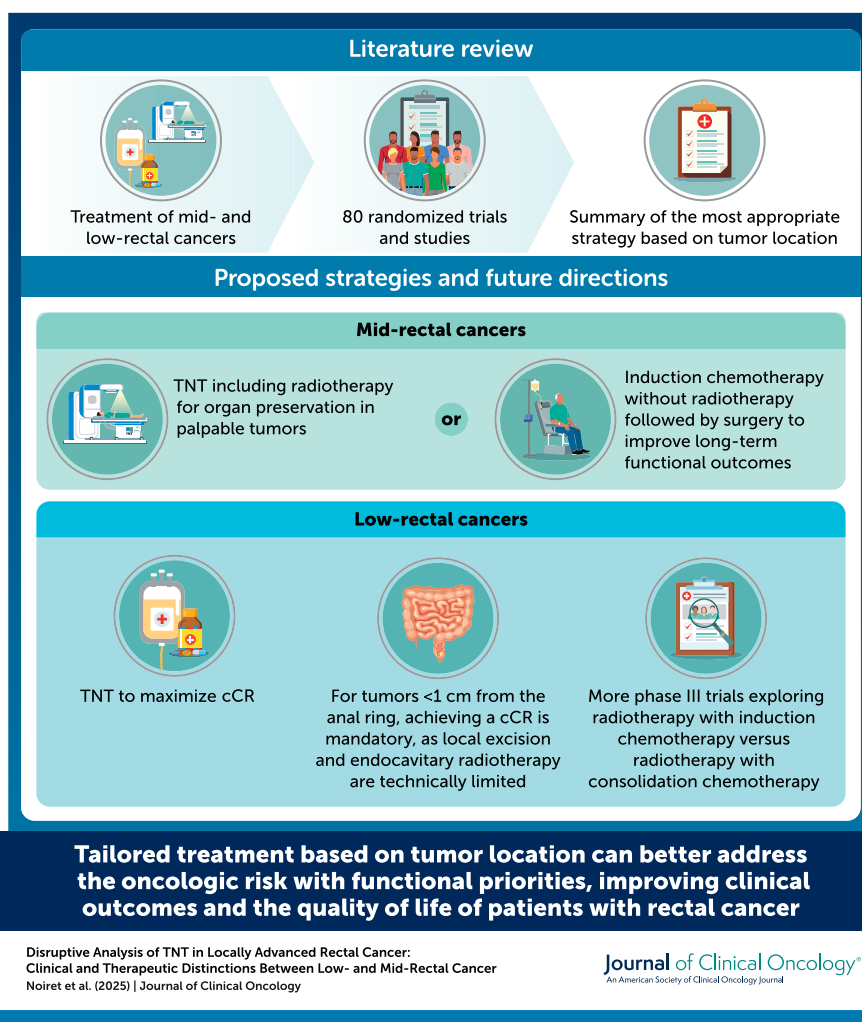
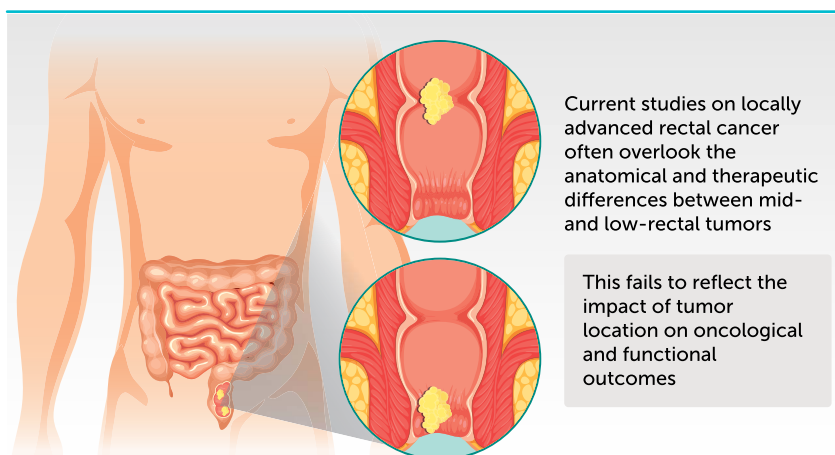


FIG 1. Therapeutic distinctions between low- and mid-rectal cancers. cCR, clinical complete response; TNT, total neoadjuvant therapy.

However, for poor responders or when NOM is the goal in mid-rectal tumors accessible to digital examination, induction or consolidation chemotherapy followed by standard CRT remains key. In particular, for mid-rectal cancers with high-risk features such as cT4 tumors, bulky nodal disease, or threatened mesorectal fascia, TNT is essential to achieve optimal local control, whereas in the NOM setting, the objective is to avoid surgery. The PRODIGE 23 trial demonstrated that INCT-CRT improved ypToNo rate (28% v 12%, $P < .001$).²³ Although induction chemotherapy may help identify candidates for subsequent CRT and possible OP, the only randomized trial comparing induction with consolidation in the setting of OP suggests that consolidation has been more successful.³² Until more data are available, the selection of the preferred TNT regimen for such purpose should be individualized and taking into consideration advantages and disadvantages of each different approach. For NOM cases, structured tumor response surveillance programs should be incorporated into surgical management, including standardized clinical, radiologic, and metabolic assessments every 2 months to optimize OP rates without compromising oncological outcomes. The feasibility of this approach has been demonstrated previously.⁹² The ongoing multicenter French randomized trial PRODIGE 101-GRECCAR 20-EVAREC trial aims to validate the role of shared decision making (SDM) in rectal cancer by comparing a tumor response surveillance program against standard tumor response assessment in OP strategies for rectal cancer (NCT 06740357). SDM empowers

patients to express their own values and priorities—whether avoiding a permanent stoma, minimizing functional impairment, or maximizing oncologic safety. Embedding SDM into routine clinical practice will be crucial to achieve not only better survival but also improved QoL.

FUTURE DIRECTIONS

This study reflects the wide variability in treatment selection between countries and centers, highlighting the importance of tailoring decisions to each case. Based on these findings, future studies should investigate mid- and low-rectal tumors separately, with an anatomic landmark between low and mid cancer located at 1 cm above the anal ring (Fig 1):

- For mid-rectal tumors, induction chemotherapy without radiotherapy should be considered to improve long-term functional outcomes if surgery is considered or INCT-CRT/CNCT-CRT when the goal is to avoid surgery.
- For low-rectal tumors, NOM is the optimal management strategy for patients who are willing to adhere to careful follow-up surveillance schedules. To optimize achievement of cCR, TNT is preferred over CRT alone, and two strategies should be explored in a phase III RCT: INCT-CRT versus CNCT-CRT with a standardized interval between TNT completion and tumor response assessment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disruptive Analysis of Total Neoadjuvant Therapy in Locally Advanced Rectal Cancer: Clinical and Therapeutic Distinctions Between Low- and Mid-Rectal Cancers

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