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The evolution of rectal cancer treatment: the journey to total neoadjuvant therapy and organ preservation

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Abstract

There has been a staggering increase in the incidence of rectal cancer, drawing our attention to early detection and optimization of its medical and surgical treatment. With this review we highlight all the major trials that revolutionized rectal cancer management and improved oncologic outcomes. We present the origins of the trimodal therapy and the studies that supported the sequence of treatment. We describe the evolution in surgical management with total mesorectal excision as the standard of care, and we review the most impactful short- vs. long-course long-course radiation therapy trials. Today, the current standard of care for non-metastatic locally advanced rectal cancer includes preoperative chemoradiation with either induction or consolidation chemotherapy, total mesorectal excision and adjuvant therapy. We discuss the advent of the "watch and wait" strategy for patients who have a complete clinical response after total neoadjuvant treatment, as well as possible future directions in the treatment of locoregional disease.

Keywords Rectal cancer, total neoadjuvant therapy, total mesorectal excision, complete clinical response

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Introduction

There has been an alarming increase in the incidence of rectal cancer in the past few decades, with rates estimated to have risen to 124.2% for adults aged 20-34 years by 2030 [1]. With this staggering rise, attention has been directed to optimizing treatment. Overall, the management of rectal cancer has improved over the past decades, leading to better oncologic outcomes. For many years, the lack of locoregional control of the disease was a major source of morbidity and mortality for patients treated with surgery alone. The advent of total mesorectal excision (TME) [2] and the addition of neoadjuvant chemoradiation (CRT) significantly reduced local recurrence [3]. Today, the current standard of care for treatment of non-metastatic locally advanced rectal cancer (LARC) includes preoperative CRT, TME and adjuvant chemotherapy (AT), though strategies are rapidly evolving. The aim of this review is to highlight the major trials that have led to the modern era of management of LARC, and to summarize the latest developments and possible future changes in the way we treat locoregional disease [1-9] (Fig. 1).

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Conflict of Interest: None

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TME and evolution of surgical approach

Surgery with curative intent for LARC consists of TME, ideally with an R0 resection [2]. This removes the mesorectal tissue that contains all perirectal lymph nodes and should control any local tumor invasion (Fig. 2). The most important predictor of local recurrence is the circumferential margin, which should be greater than 2 mm [1]. Distal margins are more debatable. Typically, if one is unable to achieve a 1-cm distal margin during a low anterior resection (LAR) for a low rectal tumor, an abdominoperineal resection is indicated. However, some data suggest that distal margins <5 mm are not associated with higher pelvic recurrence rates [1].

Though TME is the current standard of care for resecting localized rectal cancer, there is growing evidence to support

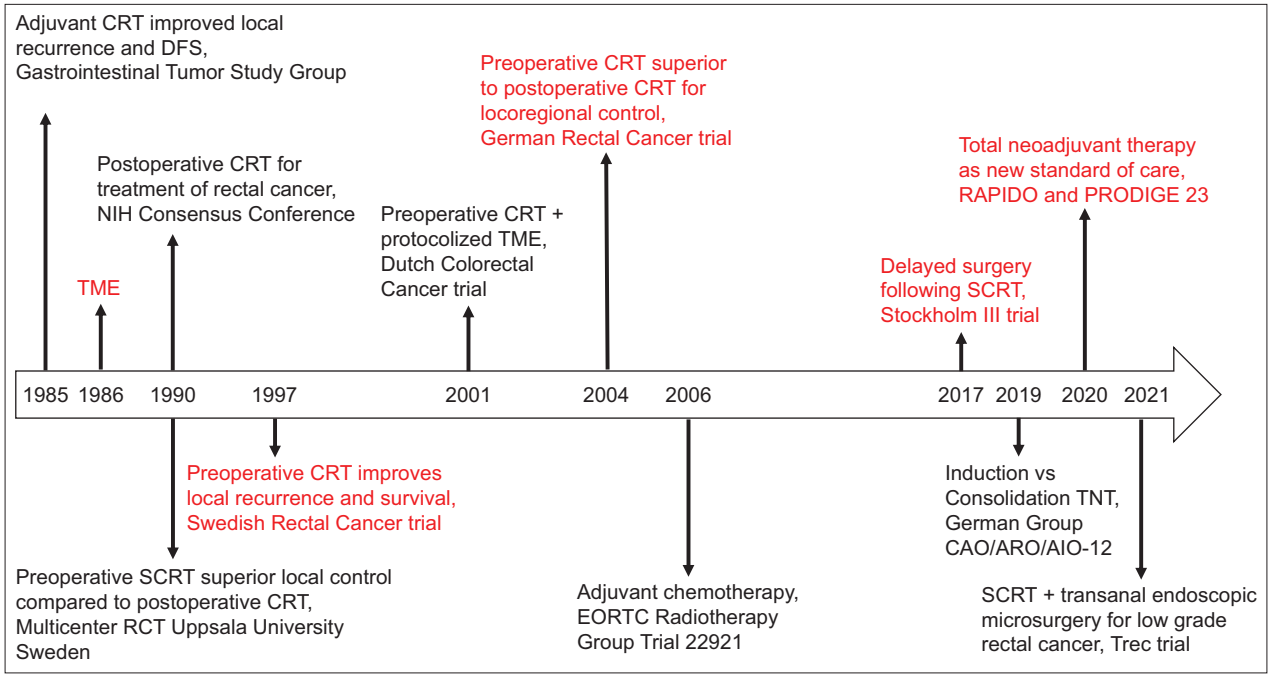

Figure 1 Timeline of the evolution of rectal cancer treatment
CRT, chemoradiation therapy; DFS, disease-free survival; RCT, randomized controlled trial; SCRT, short-course radiation therapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy

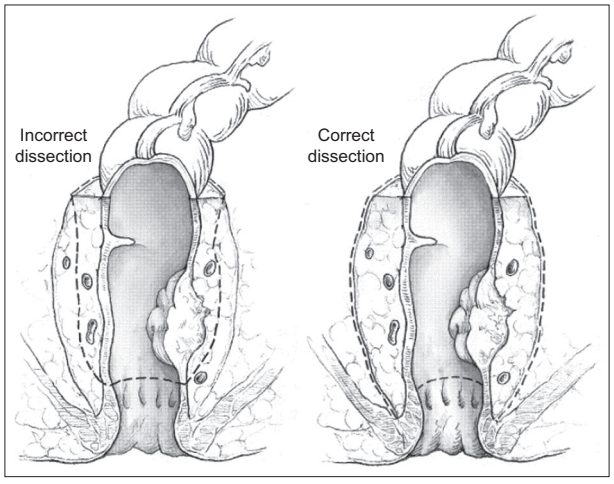

Figure 2 Total mesorectal excision (TME). Incorrect dissection (left) only incorporates a portion of the surrounding mesorectal fat. Correct dissection (right) avascular plane which contains all mesorectal fat and regional lymph nodes

alternative surgical strategies with an organ preservation approach for lower-grade rectal tumors (<T2, N0), to avoid the morbidity associated with TME. The TREC trial (Transanal Endoscopic Microsurgery [TEM] and Radiotherapy in Early rectal Cancer) showed that short-course CRT followed by TEM was able to achieve high rates of organ preservation, excellent compliance, and beneficial health-related quality of life (QoL) scores when compared to TME alone [4]. They also showed less treatment-related toxicity and no difference in disease-free survival (DFS) at 3 years [4]. Additional prospective randomized controlled trials (RCTs) are needed to further investigate long-term oncologic outcomes.

Origins of trimodal therapy

The advent of TME in 1986 significantly reduced the rate of local recurrence in patients with LARC [2]. Around this same time, the Gastrointestinal Tumor Study Group investigated the effectiveness of various adjuvant therapies in the treatment of LARC. They compared the effects of postoperative radiation therapy (RT), chemotherapy, and CRT on tumor recurrence and overall survival (OS). Patients received 4000 rads (40 Gy) delivered over 4½-5½ weeks [11]. 5-Fluorouracil (5-FU) and semustine were used as chemotherapy agents, as these were the most commonly used agents for gastrointestinal neoplasms in the late 1970s. They found significantly less local recurrence and longer DFS in patients who received adjuvant therapy compared to those who underwent surgery alone. Those treated with the combination of RT plus chemotherapy showed the most profound effects among the 3 regimens [11].

Hypoxia plays a crucial role in the tumor response to RT [12]. Oxygenated tissue is needed for radiation to induce permanent DNA damage, thus maximizing effectiveness. One study suggested that preoperative RT is more "dose effective" than postoperative RT, based on observations that higher-dose adjuvant RT is required to reduce local recurrence to the same

extent as preoperative RT [13]. However, some experts say the postoperative doses have been higher historically because of a perceived hypoxemic effect and subsequent radio-resistance in residual tissue from extensive surgery that has potentially removed oxygen-feeding blood vessels.

In 1997, the Swedish Rectal Cancer Trial was the first RCT to demonstrate a clear benefit of neoadjuvant RT compared to surgery alone [3,4,14]. Patients were randomized to receive either short-course preoperative RT (25 Gy in 5 fractions delivered in 1 week) followed by immediate surgery, or surgery alone. This study showed a significant reduction in local recurrence rates and improved 5-year OS in patients treated with preoperative RT [4] (Table 1). The Swedish Rectal Cancer trial stands alone amongst RCTs of neoadjuvant therapy for rectal cancer, revealing an OS benefit in addition to the more standard improved local control. The Swedish Rectal Cancer trial was undertaken during a period in which hospitals had not yet adopted TME approaches; therefore, neoadjuvant RT may have partially compensated for these suboptimal surgeries, portending a survival benefit. The Dutch Colorectal Cancer trial similarly compared the effects of neoadjuvant RT compared to surgery alone, with the addition of a standardized TME protocol [5,6] (Table 2). This trial showed that treatment with neoadjuvant RT, combined with an established uniform surgical approach, provides an even greater reduction in local recurrence rates [5,6]. These 2 landmark trials demonstrated that preoperative RT significantly reduced local recurrence [4-6]. Local control is further improved with the addition of 5-FU-based chemotherapy to preoperative RT [15,16].

The previously discussed advances in preoperative CRT and surgical techniques offered improvements in rates of locoregional recurrence but did not address distant metastasis, which plagues up to 30% of patients treated with curative intent and is the main cause of death from rectal cancer [17,18]. AT, intended to eradicate micrometastases, has traditionally been administered with the goal of limiting systemic recurrences. Historically, multiple studies have investigated the role of AT. However, in recent years new studies have shown conclusive evidence of the improved benefits of neoadjuvant CRT followed by TME, compared to AT. The EORTC 22921 trial first randomized patients to receive preoperative RT, with or without concomitant chemotherapy, followed by TME. It then randomized patients to receive AT (5-FU/leucovorin) or surveillance. The results did not demonstrate a statistically significant benefit with the addition of AT compared to the surveillance group in terms of OS, DFS, or risk of distant recurrence after 5 years [15]. These results were reconfirmed by the Italian trial in 2014 [19]. Other studies, such as the Chronicle trial, investigated the use of different chemotherapy agents in the adjuvant treatment arm, such as CAPOX (capecitabine/oxaliplatin), which also yielded similar results [20].

One frequently-discussed factor that probably contributes to the lack of effectiveness of AT in this setting is the low rate of regimen completion. For example, the compliance rates among the 3 aforementioned studies—EORTC 22921, Italian and CHRONICLE trials—were 43%, 55%, and 48%, respectively [15,19,20]. Many patients did not receive the recommended dose of chemotherapy in the appropriate time interval because of multiple factors, including toxicity, delays in starting treatment secondary to postoperative complications, disease progression and/or patient refusal.

The role of AT remained controversial until 2004, when the German Colorectal Study Group provided a major turning point in the treatment of patients with LARC. In this trial, patients with LARC were randomized to preoperative or postoperative CRT, with both groups also receiving AT [21]. The investigators were able to demonstrate significantly less local recurrence, lower toxicity, better overall compliance, and a better rate of sphincter preservation in patients with low-lying tumors who were treated with preoperative CRT [21] (Table 3). They failed to show a significant difference in OS. This study was widely accepted and helped shape the standard of care for treatment of LARC. For the past 20 years, the standard of care for treatment of LARC has consisted of preoperative CRT followed by TME and AT.

Table 1 Swedish rectal cancer trial

Parameter	Radiotherapy plus surgery n=553	Surgery alone n=557	P-value
Local recurrence, n (%)	63 (11)	150 (27)	0.001
Distant metastases, n (%)	84 (19)	65 (14)	-
Both local and distant recurrence, n (%)	19 (4)	47 (10)	-
5-year overall survival (%)	58	48	0.004

Radiotherapy shown to reduce local recurrence and improve 5-year survival

Table 2 Dutch colorectal study group trial

Parameter	Radiotherapy plus surgery n=897	Surgery alone n=908	P-value
Local recurrence rate (%)	2.4	8.2	0.001
Distant metastases rate (%)	14.8	16.8	0.87
Both local and distant recurrence (%)	16.1	20.8	0.09
2-year overall survival (%)	82	81.8	0.84

Further reduction in local recurrence with standardized total mesorectal excision protocol

Long- and short-course RT and timing of surgery

Though there were convincing data that preoperative RT significantly reduced the risk of local recurrence up to 50% in LARC [7], the comparative effectiveness of long- vs. short-course RT and the optimal timing of surgery remained highly debated until recent years. The conventional RT regimen implemented in most countries comprises fractionated long-course radiation (45-50.4 Gy in 1.8-2 Gy daily fractions for 5-6 weeks) combined with radio-sensitizing chemotherapy (5-FU), followed by surgery after 4-8 weeks. Short-course RT (25 Gy with 5 Gy daily fractions in 1 week, 5 days total) with surgery within 1 week was an emerging strategy being

utilized in many countries in Europe. The Stockholm III trial was a multicenter RCT that compared long-course RT with the standard expected delay for surgical treatment (4-8 weeks), short-course RT without delay, and short-course RT with delay. They observed no difference in the incidence of local recurrence, distant metastasis or OS among the 3 groups [7] (Table 4). They did, however, demonstrate significantly fewer postoperative complications in the groups that had delayed surgical treatment. Most importantly, the study re-emphasized that either short- or long-course RT with concurrent administration of chemotherapy was integral to reducing local recurrence [7].

With similar oncologic outcomes among the 3 groups, short-course RT with delay not only provides the benefit of fewer postoperative complications, but also offers a window before surgery to administer additional preoperative chemotherapy in high-risk patients. This concept is known a total neoadjuvant therapy (TNT) and was studied in the RAPIDO and PRODIGE trials, which will be discussed in further detail later in this review.

Overtreatment

After the findings of the German trial established the standard management approach to LARC, 2 challenges emerged. First, though there was a reduction in local recurrence and distant metastasis, survival rates did not improve. Second, the one-size-fits-all model led to increasing rates of side effects (toxicity of CRT and surgical adverse events) and likely overtreatment of some patients. Assessing the risk-benefit ratio of a treatment regimen and how it will affect a patient's QoL is paramount when taking care of LARC patients. An end-colostomy or a low pelvic anastomosis, for example, are both potential outcomes after surgical resection that can drastically impact and impair a patient's QoL. LAR syndrome is a collection of symptoms that patients may develop after surgical resection of the rectum, with symptoms including increased urgency, frequency, and sexual dysfunction. The prevalence of LAR syndrome can range from 20-50% [22], though there are few high-quality studies demonstrating this. Alternatively, Guillem *et al* addressed the question of how many patients with T3-node-negative rectal cancer, staged by endoscopic ultrasound or magnetic resonance imaging (MRI), actually have more advanced disease. They found that 22% of patients with cT3N0 rectal cancers had pN+ disease at time of surgery, even with neoadjuvant treatment [23]. They concluded that, despite the risk of overtreatment, preoperative CRT was warranted for early-stage cT3N0 rectal cancers [24]. Further research is still needed in this area.

Table 3 German colorectal study group trial

Parameter	Preoperative chemoradiotherapy n=415	Postoperative chemoradiotherapy n=384	P-value
Local recurrence	6%	13%	0.006
Distant recurrence	36%%	38%	0.84
Toxicity			
Acute side-effects	27%	40%	0.001
Long-term side-effects	14%	24%	0.01
Sphincter-preserving surgery performed	45/116 (39%)	15/78 (19%)	0.004
Disease-free survival	68%	65%	0.32
Overall survival	74%	76%	0.80

Acute and long-term side effects were lower in the preoperative group, particularly with respect to acute and chronic diarrhea and the development of strictures at the anastomosis. Among 194patients with tumors determined prior to randomization to require an abdominoperitoneal resection, a statistically significantly higher rate of sphincter-preserving procedures was achieved in the preoperative group

Table 4 Stockholm trial

Parameter	SRT (n=129)	SRT-delay (n=128)	LRT-delay (n=128)	P-value
Local recurrence HR (90%CI)	3 1.0 (ref)	4 1.44 (0.41-5.11)	7 2.24 (0.71-7.10)	0.48
Distant metastases HR (90%CI)	30 1.0 (ref)	38 1.40 (0.84-2.18)	35 1.20 (0.74-1.96)	0.40
Survival (5 years)	73%	76%	78%	-
Complications OR (95%CI)	65 (50%) 1.0 (ref)	48 (38%) 0.59 (0.36-0.92)	50(39%) 0.63 (0.38-1.04)	0.075

HR, hazard ratio; OR, odds ratio; CI, confidence interval; SRT, short-course radiation therapy; SRT-delay, SRT with delayed surgery; LRT-delay, long-course radiation therapy with delayed surgery

TNT

Once researchers had demonstrated that surgery can safely be delayed for 4-8 weeks following preoperative short-course RT, and that mixed evidence exists regarding AT, the next topic to investigate was the optimal timing of chemotherapy. The strategy of providing all treatment modalities (including CRT and chemotherapy) prior to surgery is known as TNT. The rationale behind TNT includes early systemic treatment, facilitating early targeting of micrometastatic disease, better compliance, less toxicity, and better tumor regression [30-33]. The complete disappearance of all tumor cells in the surgical specimen (pathologic complete response, or pCR) has been observed in up to 25% of patients who received TNT, compared to 12% who received the conventional preoperative CRT [3]. Higher pCR rates create the possibility for organ preservation in select populations.

The Polish were early leaders in TNT, aiming to improve local control. In a prospective RCT, superiority of preoperative short-course RT followed by chemotherapy, compared to standard long-course CRT, was not demonstrated in relation to DFS (43% vs. 41%, respectively, P=0.65) or OS (49% both groups) at 8 years [34]. Though not statistically significant, the results did show a trend that favored short-course radiation treatment at 3 years. This highlighted preoperative short-course RT and chemotherapy as a viable regimen for the treatment of LARC. The evidence had shown a trend that would be further investigated by the RAPIDO and PRODIGE trials, as both trials aimed to target improving local control, along with addressing distant disease.

The RAPIDO (short-course radiotherapy followed by chemotherapy before TME vs. preoperative chemoradiotherapy, TME, and optional AT in LARC), and PRODIGE (TNT with mFOLFIRINOX vs. preoperative CRT in patients with LARC) trials were 2 pivotal trials in the implementation of TNT that revolutionized the treatment of patients with LARC [8,9] (Fig. 3) (Table 5). The RAPIDO trial compared short-course RT, followed by chemotherapy and subsequent TME, to the standard neoadjuvant CRT, TME, and AT. The experimental group received short-course RT (5 Gy × 5 fractions) over 5 days. The chemotherapy for both groups consisted of CAPOX or FOLFOX4 (oxaliplatin, leucovorin [folic acid], and 5-FU), as determined by the treating physician. The standard group received long-course (2 Gy × 25 fractions) RT with concomitant capecitabine, followed by TME. An MRI-staged high-risk feature (cT4, +EMVI, cN2, or mesorectal fascial involvement) was required to be included in the study [8,9] (Fig. 3). The investigators demonstrated a statistically lower rate of disease-related treatment failure in the experimental group (20% vs. 26.8%), largely due to the reduced rate of distant metastasis [8]. The pCR rate was 28% in the experimental group vs. 14% in the standard group (P<0.001), with similar OS [8] (Table 6).

The PRODIGE 23 trial similarly compared the standard

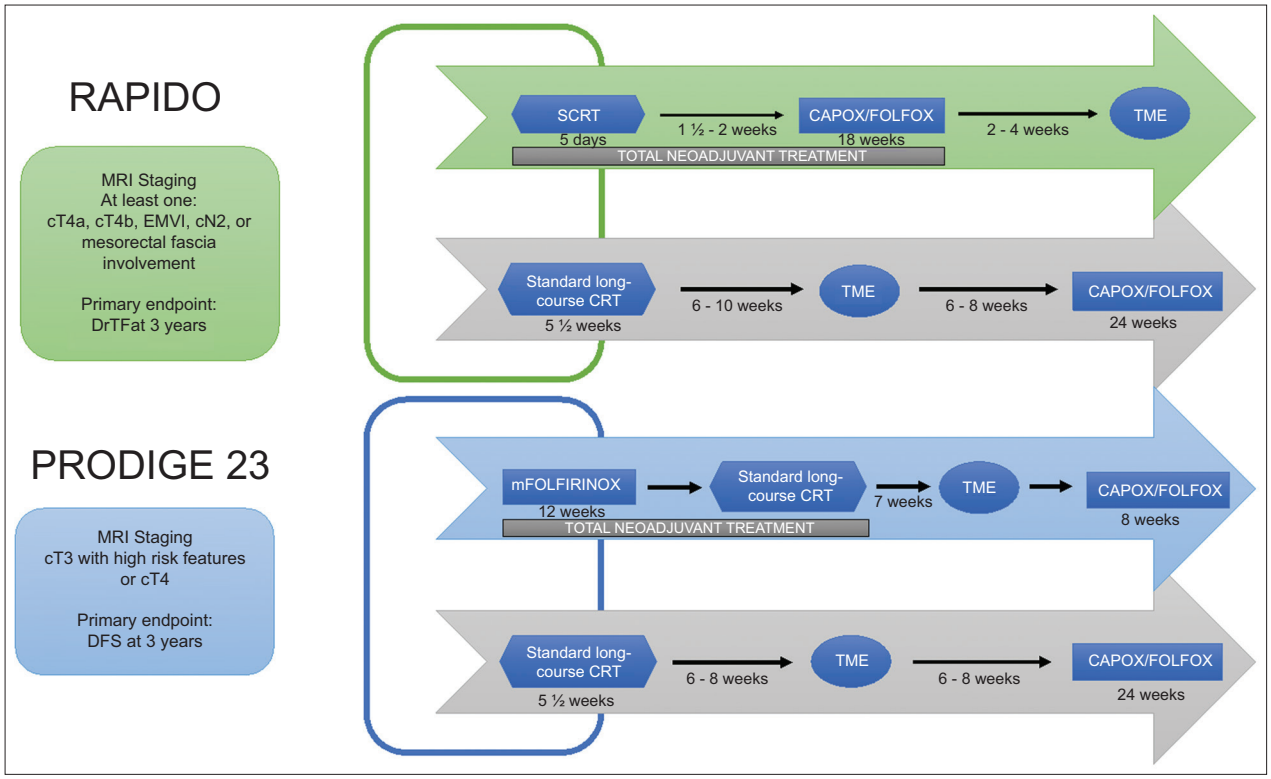

Figure 3 The 2 pivotal trials in the implementation of total neoadjuvant therapy that revolutionized the treatment of patients with locally advanced rectal cancer

CRT, chemoradiation therapy; DFS, disease-free survival; DrTF, disease-related treatment failure; EMVI, extramural venous invasion; MRI, magnetic resonance imaging; cN, clinical nodal stage; cT, clinical T stage; SCRT, short-course radiation therapy; TME, total mesorectal excision

Table 5 Patient characteristics from RADIPO and PRODIGE 23 trials

Characteristics	RAPIDO	PRODIGE 23
Number of patients	912	461
Median age (years)	62	61
Distance from anal verge		
<5 cm	25.7%	36.9%
5-10 cm	39.3%	50.3%
10-15 cm	35.0%	12.8%
Clinical T stage		
cT3	65.8%	82.2%
cT4	31.1%	12.8%
Clinical N stage		
cN0	8.4%	10.4%
cN1	26.1%	89.6%(N+)
cN2	65.5%	
Other high-risk features		
EMVI +	29.9%	NR
MRF +	61%	27%
Lateral N +	14.8%	NR

EMVI, extramural venous invasion; MRF, mesorectal fascia invasion; NR, not reported

Table 6 Comparison of outcomes from RADIPO and PRODIGE 23 trials

Outcome	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Primary endpoint	3-year DrTF 23.7% vs. 30.4%	3-year DFS 75% vs. 68.5%
pCR rate	28.4% vs. 14.3% P<0.001	27.8% vs. 12.1% P<0.001
Locoregional failure (at 3 years)	8.3% vs. 6.0% P=0.12	NR
Distant metastasis (at 3 years)	Cumulative probability 20.0% vs. 26.8%	Metastasis-free survival 78.8% vs. 71.7%
OS (at 3 years)	89.1% vs. 88.8% P=0.59	90.8% vs. 87.7% P=0.07

TNT, total neoadjuvant therapy; CRT, chemoradiation therapy; DFS, disease-free survival; DrTF, disease-related treatment failure; pCR, pathological complete response; OS, overall survival; NR, not reported

long-course CRT (2Gy × 25 fractions), followed by TME and AT, to first administering neoadjuvant chemotherapy, followed by CRT, TME and then AT [9]. The neoadjuvant regimen consisted of oxaliplatin, leucovorin, irinotecan, and 5-FU (mFOLFIRINOX). The investigators demonstrated a statistically significantly higher pCR of 27.5% in the experimental group vs. 11.7% in the standard group. Metastasis-free survival at 3 years was also significantly better in the experimental arm, at 78.8% vs. 71.7% in the standard treatment group, though there was no difference in OS [9] (Table 6). These 2 instrumental trials established TNT, not only as a safe strategy for treatment of LARC, but also as one that could reduce the incidence of distant metastases, an important goal over the last few decades.

A study by a German group (CAO/ARO/AIO-12) investigated 2 TNT regimens to better elucidate the optimal schedule of preoperative CRT and chemotherapy. This phase 2 RCT compared induction (FOLFOX followed by CRT with 5-FU plus oxaliplatin followed by TME) with consolidation therapy (up-front CRT with 5-FU plus oxaliplatin followed by FOLFOX then TME) [35]. The results showed a higher pCR in the consolidation group (25% vs. 17%). Additionally, the investigators demonstrated that the treatment modality used first with TNT had better compliance and lower toxicity. It has been theorized that induction chemotherapy could reduce the efficacy of subsequent CRT by selecting radioresistant tumor cell clones [35-37]. The consolidation therapy has the advantage of a higher pCR rate, lower toxicity, and better compliance with CRT, without affecting the subsequent chemotherapy. With the treatment goal of a curative resection, avoiding an abdominoperineal resection in low-lying tumors, and/or achieving organ preservation, TNT with the consolidation strategy may be preferable. We still lack long-term outcomes following either of the TNT strategies.

Role of organ preservation

The better treatment response with the TNT strategy has raised a novel question: do patients who have achieved a clinical CR (cCR) after TNT require surgery? As stated earlier, higher pCR rates have been established with the implementation of TNT. Intuitively, the next topic to investigate is whether removing the rectum provides any substantial benefit in patients who achieve a cCR following neoadjuvant therapy. Treating LARC non-operatively in select patients could improve long-term functional issues resulting from complications of surgery, which could significantly improve QoL.

Though the data are limited, there is some encouraging evidence regarding the feasibility of this strategy, often termed the "watch and wait" (WW) strategy. A retrospective study aimed to evaluated the oncologic outcomes of patients with LARC who received TNT (n=308), compared to those who received traditional CRT with AT (n=320) [38]. They demonstrated that more patients in the TNT group treated non-operatively achieved a cCR beyond 12 months, compared with the group treated conventionally (22% vs. 6%) [38]. A cCR was defined by a flat white scar, without ulceration or nodularity, seen endoscopically. Long-term data are still needed to assess outcomes from the TNT and WW strategies.

Organ Preservation Rectal Adenocarcinoma (OPRA) trial

The OPRA trial is a randomized phase II multicenter trial investigating the hypothesis that patients with LARC treated with TNT and TME or WW will have better 3-year DFS compared to patients treated with neoadjuvant CRT, TME and AT [39]. Patients with MRI stage T2-3, N0 or T-any, N1-2

resectable rectal cancer were randomized to receive induction FOLFOX/CAPOX before CRT or the reverse (consolidation FOLFOX/CAPOX given after CRT). Both groups were re-staged at 8-12 weeks after completing all neoadjuvant therapy. All participants underwent an extensive response evaluation via several different modalities, which included flexible sigmoidoscopy, digital rectal exam and MRI. One challenge the OPRA trial had to navigate was establishing consistent and reproducible criteria for tumor response across institutions. Memorial Sloan Kettering created a Regression Schema to assess for cCR, near-CR, or incomplete response. Patients with cCR or near-cCR were assigned to WW, and patients with an incomplete response and residual tumor underwent TME. Patients who underwent WW were followed every 3 months for 2 years, and every 6 months thereafter for surveillance [39,40]. No difference in 3-year DFS was found between the induction and consolidation groups compared to historical controls. OS was similar between induction and consolidation, though WW was used more frequently in the consolidation group. They concluded that WW in patients who achieve a cCR is a viable treatment strategy [39,40].

A new standard of care

The introduction of TNT has revolutionized the landscape for the treatment of LARC and has laid the groundwork for establishing a new standard of care. The administration of neoadjuvant FOLFOX or CAPOX after short-course RT, or upfront FOLFIRINOX followed by long-course CRT followed by surgery (consolidation or induction, respectively), are 2 treatment strategies that have been confirmed by phase III RCTs [39-44]. They have been shown to significantly improve disease-related treatment failure (largely by reducing metastatic recurrences) while improving DFS. Additionally, these regimens achieve both better pCR, associated with improved rates of recurrence and survival, as well as better cCR, allowing for non-operative management with the WW strategy. Patient selection and assessment of tumor response via cross-sectional imaging and endoscopic surveillance are key to a successful WW strategy [39,40,45-47].

Concluding remarks

Over the last 40 years, the treatment of rectal cancer has changed dramatically. Through advancements in surgical techniques, preoperative CRT and optimal timing of surgery, we have improved local recurrence and DFS. The inability to improve distant recurrence was finally addressed with the emergence of TNT. Both TNT induction and consolidation regimens have been shown to be effective and are being further investigated. TNT is now an established treatment of LARC, as it has been shown to offer improved survival, reduce local and distant recurrence rates, and potentially open the door for non-operative strategies. Patients managed non-operatively might avoid the morbidity and QoL implications associated with rectal surgery. Future studies to investigate the molecular and oncologic differences between partial and complete responders are warranted to identify patients who will respond to TNT and may benefit from non-operative management.

References

1. Keller DS, Berho M, Perez RO, Wexner SD, Chand M. The multidisciplinary management of rectal cancer. *Nat Rev Gastroenterol Hepatol* 2020;**17**:414-429.
2. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;**1**:1479-1482.
3. Papaccio F, Roselló S, Huerta M, et al. Neoadjuvant chemotherapy in locally advanced rectal cancer. *Cancers (Basel)* 2020;**12**:3611.
4. Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N; Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;**336**:980-987.
5. van Gijn W, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;**12**:575-582.
6. Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo) radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol* 2015;**26**:696-701.
7. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol* 2017;**18**:336-346.
8. Bahadoer RR, Dijkstra EA, van Etten B, et al; RAPIDO collaborative investigators. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:29-42.
9. Conroy T, Lamfichekh N, Etienne PL, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: Final results of PRODIGE 23 phase III trial, a UNICANCER GI trial. *J Clin Oncol* 2020;**38**(Suppl:4007).
10. Bach SP, Gilbert A, Brock K, et al; TREC collaborators. Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. *Lancet Gastroenterol Hepatol* 2021;**6**:92-105.
11. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985;**312**:1465-1472.
12. Kuperman VY, Lubich LM. Effect of reoxygenation on hypofractionated radiotherapy of prostate cancer. *Med Phys* 2020;**47**:5383-5391.
13. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**:638-646.
14. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin*

Oncol 2005;**23**:5644-5650.
15. Bosset JF, Collette L, Calais G, et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;**355**:1114-1123.
16. Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): Final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015;**16**:979-989.
17. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;**30**:1926-1933.
18. Elferink MA, van Steenbergen LN, Krijnen P, et al; Working Group Output of the Netherlands Cancer Registry. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. *Eur J Cancer* 2010;**46**:1421-1429.
19. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014;**113**:223-229.
20. Glynne-Jones R, Counsell N, Quirke P, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol* 2014;**25**:1356-1362.
21. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731-1740.
22. Pieniowski EHA, Nordenvall C, Palmer G, et al. Prevalence of low anterior resection syndrome and impact on quality of life after rectal cancer surgery: population-based study. *BJS Open* 2020;**4**:935-942.
23. Guillem JG, Díaz-González JA, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. *J Clin Oncol* 2008;**26**:368-373.
24. Kachnic LA, Hong TS, Ryan DP. Rectal cancer at the crossroads: the dilemma of clinically staged T3, N0, M0 disease. *J Clin Oncol* 2008;**26**:350-351.
25. Ciseł B, Pietrzak L, Michalski W, et al; Polish Colorectal Study Group. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. *Ann Oncol* 2019;**30**:1298-1303.
26. Fokas E, Allgäuer M, Polat B, et al; German Rectal Cancer Study Group. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. *J Clin Oncol* 2019;**37**:3212-3222.
27. Ludmir EB, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: an emerging option. *Cancer* 2017;**123**:1497-1506.
28. Fokas E, Ströbel P, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy as a prognostic factor and individual-level surrogate for disease-free survival in rectal cancer. *J Natl Cancer Inst* 2017;**109**.
29. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol* 2018;**4**:e180071.
30. Smith JJ, Chow OS, Gollub MJ, et al. Organ preservation in rectal adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. *BMC Cancer* 2015;**15**:767.
31. Gérard JP, Barbet N, Gal J, et al. Planned organ preservation for early T2-3 rectal adenocarcinoma: A French, multicentre study. *Eur J Cancer* 2019;**108**:1-16.
32. Stringfield SB, Fleshman JW. Specialization improves outcomes in rectal cancer surgery. *Surg Oncol* 2021;**37**:101568.
33. Kavalukas SL, Ghuman A, Sharp SP, Wexner SD. Robotic or laparoscopic surgery for rectal cancer - which is the best answer? a comprehensive review of non-oncological outcomes and learning curve. *Mini-invasive Surg* 2020;**4**:61.
34. Petrelli F, Trevisan F, Cabiddu M, et al. Total neoadjuvant therapy in rectal cancer a systemic review and meta-analysis of treatment outcomes. *Ann Surg* 2020;**271**:440-448.
35. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol* 2008;**26**:778-785.
36. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019;**144**:1941-1953.
37. Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol* 2019;**13**:109-131.
38. Glynne-Jones R, Grainger J, Harrison M, Ostler P, Makris A. Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: Should we be more cautious? *Br J Cancer* 2006;**94**:363-371.
39. van der Valk MJM, Marijnen CAM, van Etten B, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer – Results of the international randomized RAPIDO-trial. *Radiother Oncol* 2020;**147**:75-83.
40. Neuman HB, Patil S, Fuzesi S, et al. Impact of a temporary stoma on the quality of life of rectal cancer patients undergoing treatment. *Ann Surg Oncol* 2011;**18**:1397-1403.
41. Conroy T, Bosset JF, Etienne PL, et al; Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (PRODIGE) Group. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:702-715.
42. Anker CJ, Buckstein MH, Chuong MD, et al. The evolving personalized landscape of colorectal cancer therapies. *Int J Radiat Oncol Biol Phys* 2021;**110**:1255-1262.
43. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. *J Natl Cancer Inst* 2015;**107**:djv248.
44. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;**28**(Suppl_4):iv22-iv40.
45. Ruppert R, Kube R, Strassburg J, et al; other members of the OCUM Group. Avoidance of overtreatment of rectal cancer by selective chemoradiotherapy: results of the Optimized Surgery and MRI-Based Multimodal Therapy trial. *J Am Coll Surg* 2020;**231**:413-425.
46. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol* 2019;**5**:e185896.
47. Påhlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. *Ann Surg* 1990;**211**:187-195.