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Current Trends in the Treatment of Locally Advanced Rectal Cancer: Where We Are and How We Got Here

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Abstract

Purpose of Review The trimodal treatment for LARC—surgery, radiotherapy, and chemotherapy—has been the standard of care for more than 30 years but is facing fresh challenges. Major contemporary developments include the delivery of full systemic chemotherapy in the preoperative period, with or without chemoradiation (total neoadjuvant therapy or "TNT"), and the withholding of surgery for patients who achieve a complete clinical response (cCR) to initial treatment ("watch-and-wait"). We review the historical development of these trends and propose an approach to LARC treatment that integrates newly emerging protocols with the traditional standard of care.

Recent Findings Data from the recent randomized trials PRODIGE 23 and CAO/ARO/AIO-12 show that patients with LARC treated with TNT have a higher frequency of cCR, longer disease-free survival, and increased ability to tolerate chemotherapy. Preliminary results of the prospective OPRA study indicate that a watch-and-wait approach may permit sphincter preservation for a high proportion of patients without compromising survival.

Summary The increasing adoption of TNT to treat LARC is due to high rates of cCR, low levels of toxicity, a superior ability to deliver full-dose chemotherapy, and better preservation of quality of life. Based on current evidence, the combination of preoperative systemic chemotherapy and non-surgical management is appropriate for selected patients who have achieved a cCR and face a high risk of sphincter loss or dysfunction with surgery.

Keywords Locally advanced rectal cancer · Total neoadjuvant therapy · Watch-and-wait · Short-course radiation therapy · Long-course radiation therapy

Introduction

The first treatment protocol for locally advanced rectal cancer (LARC) to receive the imprimatur of a "standard of care" is now more than 30 years old. In 1990, the NIH Consensus Conference, after a review of the clinical research to date, offered this unambiguous summary: "Combined postoperative chemotherapy and radiation therapy improves local control and survival in stage II and III patients and is recommended [1]." At the heart of that recommendation was the adoption of the emerging multidisciplinary approach to medicine, and the embrace of a trimodal treatment plan—the combined use of surgery, radiotherapy, and chemotherapy—appearing to signal that the future of medicine had arrived. Curiously, though, while the multidisciplinary approach dominates medicine now more than ever, the conventional trimodal treatment for LARC is now facing challenges from each of the disciplines. The management of LARC is on a path "back to the future," a path that is leading to the strategic reintroduction of bimodal and unimodal treatment protocols once left behind.

Two essential aspects of contemporary rectal cancer management are driving the changes that are taking place. The first is that progress in the prevention of local recurrences for advanced rectal cancers has not been matched by a comparable reduction in distant tumor recurrences and cancer-related deaths. Intensification of treatment is the inevitable result, bringing new concerns about over treating patients who might have done just as well on the old regimen. In this way,

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a second theme, risk stratification, assumes a central role. Refinement of risk stratification is an ever-expanding part of contemporary medicine, aided by better imaging techniques, insights from tumor biology, and greater precision in patient profiling. The historical record for LARC highlights both of these themes: the requirement for intensified treatment is one factor in the clinical appeal of "total neoadjuvant therapy," and the reliance on risk stratification to lower treatment-related morbidity has provided impetus for the non-surgical option called "watch-and-wait," reviewed in Table 1.

The Evolution of a Standard of Care for LARC

In the nineteenth century, surgery for rectal cancer produced a high percentage of perioperative deaths, and surviving patients could anticipate a very brief survival marred by a permanent colostomy. A major step forward in surgical technique was taken with the introduction of radical abdominoperineal resection by William Ernest Miles, in 1908 [2]. Postoperative deaths diminished, but the prognosis of LARC remained poor. For cancer invading the muscle wall (stage II) or infiltrating regional lymph nodes (stage III), the local recurrence (LR) rate was about 25–50% [3, 4]. As late as 1980, only one-half of patients remained alive 5 years after surgery [5]. Once LR occurred, bringing with it an unavoidable decline in quality of life, median survival was 12–18 months [6].

The pathological studies of Philip Quirke [7, 8], which began to appear in the 1980s, demonstrated that the risk of LR could be predicted by inspection of the circumferential margin of resected tumor specimens [9, 10]. Inspired by this evidence, the English surgeon Richard Heald abandoned the century-old practice of blunt, manual dissection and introduced a novel surgical technique, brought into its final form after 500 consecutive operations [11]. Total mesorectal excision (TME) involved sharp excision along the tissue planes of the mesorectum, followed by the removal en bloc of the rectal fascia with its associated vascular, lymphatic, and perineural tissue [3]. Employing TME, with only an occasional contribution from adjuvant therapy (which he treated dismissively), Heald reported an astounding 20-year LR rate of 2%. In 1998, when he published this result, he could perceive no future for rectal cancer treatment outside the operating theater: "Multimodality therapies," he wrote, "[…] will not be necessary when more money is available for surgical time and training" [11].

But while Heald's technique permeated all of Europe, his treatment philosophy did not. As early as 1975, the Swedish Rectal Cancer Group was treating patients experimentally with preoperative short-course hypofractionated RT (SCRT)—25 Gy in 5 daily fractions followed 1 week later by surgical resection [12–19]. One study performed in the pre-TME era was remarkable for the finding that 5-year survival increased from 48 to 58%—perhaps the only RT study for LARC that has ever demonstrated a survival benefit. SCRT was also shown to reduce LR from 27 to 11% [20, 21], an improvement maintained on long-term follow-up [22]. This improvement in LR was duplicated after TME was firmly installed as the universally preferred surgical option, putting to rest the hypothesis that the advent of TME had rendered LARC, once and for all, a strictly surgical disease [3, 23].

By introducing radiotherapy (RT) or chemotherapy into the preoperative period, the early clinical investigations of adjuvant therapy were following a precedent already laid down by the Swedish group. This preference for neoadjuvant intervention is unsurprising, as many theoretical considerations and clinical observations support it: (1) RT delivered preoperatively can be contoured to tumor masses undisturbed by surgery; (2) tissue oxygenation (and therefore radiosensitivity) is greater before surgery has disrupted the vessels in the tumor bed; (3) tumor masses are easier to remove if they have been shrunk by RT; (4) RT reduces dissemination of cancer cells during surgical dissection; and (5) RT delivered preoperatively improves the integrity of surgical anastomoses, limits radiation exposure of the small bowel and, in the case of low-lying rectal tumors, permits more sphincter-sparing procedures. Added to these is the pragmatic consideration that a short, preoperative RT schedule has demonstrable benefits for hospital budgets, clinician workloads, and patient compliance.

But a convincing argument could also be made for postoperative adjuvant therapy, which began to dominate clinical investigations in the 1980s and to shape clinical practice, especially in the USA. A major reason for that domination, and one that has retained its relevance, was the opportunity for risk stratification. When surgery is the first stage of treatment, a pathologic specimen is available to decide the merit of proceeding to RT and chemotherapy (it is the same argument that will be turned on its head when the response to intensive chemotherapy and/or radiation is used to decide the merit of proceeding to *surgery*). When the NIH Conference took up the challenge of establishing a standard of care for LARC, in 1990, studies of the postoperative school were dominant, led by reports from the Gastrointestinal Tumor Study Group [24–26] and similar randomized trials from the North Central Cancer Treatment Group (NCCTG) [27], the National Adjuvant Surgical Breast and Bowel Project (NASBP)-R01 [28], and the Medical Research Council [29, 30]. These studies demonstrated improved local control and OS following postoperative long-course radiotherapy (LCRT)—i.e., 45–50.4 Gy in 25–28 fractions administered 6–8 weeks after surgery. When fluoropyrimidine-based chemotherapy was added to the postoperative regimen, local control improved even more [27, 31], and high-risk patients lived longer [32–34]. The results pointed uniformly to a standard of care that incorporated postoperative

Table 1 Major prospective trials evaluating TNT

Study	Setting	Randomization	Median follow-up	Results	Interpretation
Maréchal *Ann Oncol 2012*	Multicenter, phase II randomized trial *N* = 57 cT2-T4 N +	A: CRT (45 Gy/25 + 5-FU) → TME B: mFOLFOX6 → CRT (45 Gy/25 + 5-FU) → TME	–	pCR: A: 28%; B: 25% ($p = 0.92$) *(TME 6–8 weeks after CRT)*	Induction CT is feasible in LARC patients without compromising the preoperative CRT completion but no locoregional benefit over standard therapy
Chua *Lancet Oncol 2010*	Phase II single-arm trial *N* = 105 T3-T4 and T1–4 N2	CAPOX × 12 weeks → CRT (54 Gy/6 weeks + capecitabine) → TME → capecitabine × 12 weeks	55 months	pCR: 20% *(TME 6 weeks after CRT)* 3-year PFS: 68% 3-year OS: 83%	Intensification of systemic therapy with neoadjuvant combination CT before standard treatment is feasible in poor-risk, potentially operable rectal cancer with acceptable safety and promising long-term outcomes
Spanish GCR-3 Fernandez-Martos *J Clin Oncol 2010* *Ann Oncol 2015*	Phase II randomized trial *N* = 108 Distal/middle third tumor, T3-4 and/or N +	A: CRT (50.4 Gy/28 + CAPOX) → TME → CAPOX × 4 cycles B: CAPOX × 4 cycles → CRT (50.4 Gy/28 + CAPOX) → TME	69.5 months	5-year DFS: A: 64%; B: 62% ($p = 0.85$) 5-year OS: A: 78%; B: 75% ($p = 0.64$) 5-year LR: A: 2%; B: 5% ($p = 0.61$) 5-year DM: A: 21%; B: 23% ($p = 0.79$) pCR: A: 13%; B: 14% ($p = 0.94$) G3/4 toxicity during chemo: A: 54%; B: 19% ($p = 0.0004$) Compliance with study protocol: A: 54%; B: 91% ($p < 0.0001$)	Induction CT has similar pCR, increased compliance, and lower toxicity compared to adjuvant CT
TIMING Garcia-Aguilar *Ann Surg 2011* *Lancet Oncol 2015*	Multicenter, phase II non-randomized trial *N* = 259 T3-4 or N1-2, within 12 cm of anal verge	A: CRT (50.4 Gy/28 + 5-FU) → TME B: CRT (50.4 Gy/28 + 5-FU) → 2/4/6 cycles mFOLFOX → TME	–	pCR: 0 cycles: 18% 2 cycles: 25% 4 cycles: 30% 6 cycles: 38% No differences in G3 + surgical complications, G3 + chemo-associated AE increased with increased number of cycles *(A: TME 6–8 weeks after CRT, B: TME 3–5 weeks after mFOLFOX)*	This TNT regimen resulted in a doubling of pCR with 6 cycles of mFOLFOX
CONTRE Perez *Am J Clin Oncol 2017*	*N* = 39 T3-T4 and/or N1-N2	mFOLFOX6 × 8 cycles → CRT (capecitabine + 50.4 Gy/28) → TME	25.5 months	pCR: 33% *(TME 6–10 weeks after CRT)* 89% of patients complete TNT	TNT is well-tolerated

Table 1 (continued)

Study	Setting	Randomization	Median follow-up	Results	Interpretation
COPERNICUS Gollins *Br J Cancer 2018*	Multicenter, phase II single-arm trial *N* = 57 T3a-b and EMVI or mesorectal LNs, T3c-d or T4a	Oxaliplatin/5-FU × 8 weeks → RT (25 Gy/5) → TME → oxaliplatin/5-FU or CAPOX × 16 weeks	27 months	Post-NAC MRI at 9 weeks showed 73% were T-down-staged 2-year PFS: 86.2%	Regimen was well tolerated with effective downstaging and encouraging PFS
German CAO/ARO/AIO-12 Fokas *J Clin Oncol 2019*	Multicenter, phase II randomized trial *N* = 306 cT3-T4 or N +	A: FOLFOX × 3 cycles → CRT (50.4 Gy/28 + 5-FU + oxaliplatin) → TME B: CRT (50.4 Gy/28 + 5-FU + oxaliplatin) → FOLFOX × 3 cycles → TME	4 years	pCR: A: 17%; B: 25% *(Median time from end of CRT to surgery: 45 vs 90 days, respectively)* CRT-related grade 3/4 toxicity: A: 37%; B: 27% CRT compliance: A: 91%; B: 97%	CT delivered after CRT produced less toxicity and more frequent pCR than CT delivered before CRT
Polish II Bujko *Ann Oncol 2016,* Ciseł *Ann Oncol 2019*	Randomized trial *N* = 515 cT4 or fixed cT3	A: SCRT (25 Gy/5) → FOLFOX4 × 3 cycles → TME B: CRT (50.4 Gy/28 + FOLFOX) → TME	7 years	8-year OS: 49% in both groups 8-year DFS: A: 43%; B: 41% ($p = 0.65$) 8-year LF: A: 35%; B: 32% ($p = 0.60$) 8-year DM: A: 36%; B: 34% ($p = 0.54$) Late grade 3 + toxicity: A: 11%; B: 9% ($p = 0.66$)	Preoperative SCRT + chemo was not superior to standard CRT
STELLAR Jin 2015, Jin 2017, Jin 2021 **Abstracts, publication pending*	Multicenter, phase III non-inferiority randomized trial *N* = 599 Distal or middle third tumor, T3-T4 and/or N +	A: SCRT (25 Gy/5) → CAPOX × 4 cycles → TME → CAPOX × 2 cycles B: CRT (50 Gy/25 + capecitabine) → TME → CAPOX × 6 cycles	35 months	3-year DFS: A: 64.5%; B: 62.3% (HR 0.883, $p < 0.001$) 3-year OS: A: 86.5%; B: 75.1% ($p = 0.036$) pCR: A: 16.6%; B: 11.8% ($p = 0.134$) pCR + cCR: A: 22.5%; B: 12.6% ($p = 0.001$) *(TME 6–8 weeks after preoperative treatment)*	SCRT combined with sequential chemotherapy was noninferior to CRT. SCRT combined with chemotherapy presented a higher cCR + pCR and 3-year OS compared with CRT; long-term results are pending
PRODIGE 23 Conroy *Lancet Oncol 2021*	Multicenter, phase III randomized trial *N* = 461 cT3-T4, N0-2, < 15 cm from the anal verge	A: FOLFIRINOX × 6 cycles → CRT (50 Gy/25 + capecitabine) → TME → CT (mFOLFOX6) B: CRT (50 Gy/25 + capecitabine) → TME → CT (mFOLFOX6)	46.5 months	pCR: A: 28%; B: 12% ($p < 0.0001$) *(TME 6–8 weeks after CRT)* 3-year DFS: A: 76%; B: 69% ($p = 0.034$) 3-year OS: A: 91%; B: 88% ($p = 0.08$)	NAC prior to standard preoperative CRT produced a significant improvement in pCR and DFS

Table 1 (continued)

Study	Setting	Randomization	Median follow-up	Results	Interpretation
RAPIDO Bahadoer *Lanc Oncol 2021*	Multicenter, phase III rand-omized trial $N = 920$ cT4, N2, < 1 mm to MRF, EMVI, or lateral nodes > 1 cm	A: SCRT (25 Gy/5) → CAPOX × 6 cycles or FOLFOX4 × 9 cycles → TME B: CRT (50.4 Gy/28 or 50 Gy/24) + capecitabine → TME → CAPOX × 8 cycles or FOLFOX4 × 12 cycles	4.6 years	3-year disease-related treatment failure: A: 23.7%; B: 30.4% ($p = 0.019$) 3-year DM: A: 20%; B: 26.8% ($p = 0.0048$) 3-year LRF: A: 8.3%; B: 6.0% ($p = 0.12$)	SCRT followed by CT and surgery resulted in less disease-related treatment failure than CRT followed by surgery and adjuvant CAPOX

CT, chemotherapy; *CRT*, chemoradiation; *RT*, radiation therapy; *SCRT*, short-course radiation therapy; *LCRT*, long-course radiation therapy; *NAC*, neoadjuvant chemotherapy; *EMVI*, extramural vascular invasion; *MRF*, mesorectal fascia; *HR*, hazard ratio; *TME*, total mesorectal excision; *OS*, overall survival; *PFS*, progression-free survival; *RFS*, relapse-free survival; *LF*, local failure; *LRF*, locoregional failure; *LR*, local recurrence; *LC*, local control; *DM*, distant metastases; *AE*, adverse events; *pCR*, pathologic complete response; *cCR*, clinical complete response

chemoradiation. Major trials (Intergroup 0147 and NSABP R-03 [35]) that followed the Swedish model and required a treatment arm delivering preoperative chemoradiation closed early due to poor accrual.

In Europe, however, interest in neoadjuvant therapy had not waned and had actually gathered strength due to studies from France (FFCD 920) [36], Poland [37, 38], the Netherlands [3], and the EORTC [39–41], as well as from several meta-analyses [20, 21]. These reports demonstrated that a protocol of preoperative RT and 5-fluoropyrimidine-based chemotherapy resulted in more tumor downstaging and better local control than surgery or RT alone. All these trials employed long-course chemoradiation (CRT)—short-course RT is not given with concurrent chemotherapy—and they achieved a pathologic complete response (pCR) in about 10–30% of patients [42, 43]. As with postoperative CRT, however, a reduction in distant metastases and cancer-related deaths remained elusive.

For many clinicians, the uncertainty surrounding alternative forms of CRT ended when the German CAO/ARO/AIO 94 study was published in 2004 [44]. Five-year cumulative incidence of local relapse of LARC was reported to be 6% using postoperative CRT and 13% using preoperative CRT—a difference maintained at 11-year follow-up [45]. Distant recurrences and OS did not differ, but treatment-related toxicity was less with the neoadjuvant protocol, and the rate of sphincter preservation for patients undergoing abdominoperineal resections was increased. Later, the LYON 96–02 study provided further evidence favoring the neoadjuvant approach, confirming an improved rate of sphincter preservation for low-lying rectal tumors [46, 47]. Studies by the UK Medical Research Council [30, 48, 49] and the Colorectal Cancer Collaborative Group [21], among others [50, 51] supported preoperative intervention, while based partly on the precedent of colon cancer, postoperative chemotherapy took on the role it has since retained as a potential asset for high-risk patients [52–54]. After a transitional period lasting several years, neoadjuvant chemoradiation followed by TME, with an ancillary role for adjuvant chemotherapy, became for much of the world the new standard of care [49, 53, 55–58].

SCRT vs LCRT

While postoperative chemoradiation receded as an option for LARC, controversy arose regarding the optimal neoadjuvant RT regimen [59]. Long-course chemoRT (LCRT), as practiced in the USA, and short-course RT (SCRT), as pioneered in Sweden, achieve very similar local control, sphincter preservation, and OS [37, 38, 60]. Trials including both SCRT and LCRT are reviewed in Table 2.

Table 2 Major prospective trials evaluating SCRT vs LCRT

Study	Setting	Randomization	Median follow-up	Results	Interpretation
Polish I Bujko *Radiother Oncol 2004* *Br J Surg 2006*	Multicenter, randomized trial *N* = 312 cT3-4 without sphincter involvement	A: SCRT (25 Gy/5) → TME B: CRT (50.4 Gy/28 + 5-FU + leucovorin) → TME	48 months	Early grade 3/4 radiation toxicity: A: 3.2%; B: 18.2% ($p < 0.001$) No difference in sphincter preservation rate, 4-year OS, DFS, LC, or severe late toxicity	CRT did not increase survival, local control, or late toxicity compared with SCRT alone
Stockholm III Erlandsson *Lancet Oncol 2017* *Radiother Oncol 2019*	Multicenter, phase III randomized non-inferiority trial *N* = 840 Resectable rectal cancer	A: SCRT (25 Gy/5) → TME *(1 week after completing RT)* B: SCRT (25 Gy/5) → TME *(4–8 weeks after completing RT)* C: RT (50 Gy /25) → TME *(4–8 weeks after completing RT)*	5.2 years	*Analysis arm A vs B vs C:* pCR: A: 0.3%; B: 10.4%; C: 2.2% ($p < 0.0001$) No differences in frequency of postoperative complications, LC, DM, or OS *Analysis arm A vs B:* Any postoperative complication: A: 53%; B: 41% ($p = 0.001$) Any surgical complication: A: 36%; B: 28% ($p = 0.03$)	Similar oncological results between SCRT with immediate surgery, SCRT with delayed surgery, and LCRT. SCRT with delayed surgery induces more tumor regression and pCR compared to LCRT. SCRT with delay to surgery is a useful alternative to conventional SCRT with immediate surgery due to reduced postoperative complications
TROG 01.04 Ngan *JCO 2012* *Ann Surg 2017*	Multicenter, randomized trial *N* = 326 cT3N0-2, < 12 cm from anal verge	A: SCRT (25 Gy/5) → TME → 5-FU × 6 cycles B: CRT (50.4 Gy/5 + 5-FU) → TME → 5-FU × 4 cycles	6 years	Grade 3/4 toxicity: A: 1.9%; B: 27.1% ($p < 0.001$) No difference in postoperative complications	LCRT had significantly higher AEs compared with SCRT with no significant differences in postoperative complications
Polish II Bujko *Ann Oncol 2016,* Ciseł *Ann Oncol 2019*	Randomized trial *N* = 515 cT4 or fixed cT3	A: SCRT (25 Gy/5) → FOLFOX4 × 3 cycles → TME B: CRT (50.4 Gy/28 + FOLFOX) → TME	7 years	8-year OS: 49% in both groups 8-year DFS: A: 43%; B: 41% ($p = 0.65$) 8-year LF: A: 35%; B: 32% ($p = 0.60$) 8-year DM: A: 36%; B: 34% ($p = 0.54$) Late grade 3 + toxicity: A: 11%; B: 9% ($p = 0.66$)	Preoperative SCRT + chemo was not superior to standard CRT
STELLAR Jin 2015 Jin 2017 Jin 2021 **Abstracts, publication pending*	Multicenter, phase III non-inferiority randomized trial *N* = 599 Distal or middle third tumor, T3-T4 and/or N +	A: SCRT (25 Gy/5) → CAPOX × 4 cycles → TME → CAPOX × 2 cycles B: CRT (50 Gy/25 + capecitabine) → TME → CAPOX × 6 cycles	35 months	3-year DFS: A: 64.5%; B: 62.3% (HR 0.883, $p < 0.001$) 3-year OS: A: 86.5%; B: 75.1% ($p = 0.036$) pCR: A: 16.6%; B: 11.8% ($p = 0.134$) pCR + cCR: A: 22.5%; B: 12.6% ($p = 0.001$) *(TME 6–8 weeks after preoperative treatment)*	SCRT combined with sequential CT was noninferior to CRT. SCRT combined with CT presented a higher cCR + pCR and 3-year OS compared with CRT; long-term results are pending

Table 2 (continued)

Study	Setting	Randomization	Median follow-up	Results	Interpretation
RAPIDO Bahadoer *Lanc Oncol 2021*	Multicenter, phase III randomized trial $N = 920$ cT4, N2, < 1 mm to MRF, EMVI, or lateral nodes > 1 cm	A: SCRT (25 Gy/5) → CAPOX × 6 cycles or FOLFOX4 × 9 cycles → TME B: CRT (50.4 Gy/28 or 50 Gy/24) + capecitabine → TME → CAPOX × 8 cycles or FOLFOX4 × 12 cycles	4.6 years	3-year disease-related treatment failure: A: 23.7%; B: 30.4% ($p = 0.019$) 3-year DM: A: 20%; B: 26.8% ($p = 0.0048$) 3-year LRF: A: 8.3%; B: 6.0% ($p = 0.12$)	SCRT followed by CT and surgery resulted in less disease-related treatment failure than CRT followed by surgery and adjuvant CAPOX

CT, chemotherapy; *CRT*, chemoradiation; *RT*, radiation therapy; *SCRT*, short-course radiation therapy; *LCRT*, long-course radiation therapy; *NAC*, neoadjuvant chemotherapy; *EMVI*, extramural vascular invasion; *MRF*, mesorectal fascia; *HR*, hazard ratio; *TME*, total mesorectal excision; *OS*, overall survival; *PFS*, progression-free survival; *RFS*, relapse-free survival; *LF*, local failure; *LRF*, locoregional failure; *LR*, local recurrence; *LC*, local control; *DM*, distant metastases; *AE*, adverse events; *pCR*, pathologic complete response; *cCR*, clinical complete response

A notable exception to the clinical equivalence of LCRT and SCRT is the higher incidence of pCR produced by the long-course protocol [61, 62], a difference likely attributable at least in part to the duration of the surgical waiting periods—typically 1 week for SCRT versus 6–8 weeks for LCRT. Acute toxicity is reportedly lower with SCRT, but toxicity may be confounded with surgical complications when radiotherapy is followed immediately by a resection. Tumor downstaging has become a closely examined benefit of neoadjuvant therapy and is minimal when surgery is delayed less than 4 weeks [63]. The effect of longer delays, however, is less predictable. GRECCAR-6 found that extending the surgical delay after CRT from 7 to 11 weeks had no effect on oncologic outcome but did increase surgical morbidity [64]. Other studies have found that delays greater than 13 weeks [63], or even 20 weeks [65, 66], produce incremental tumor regression. These data are difficult to reconcile, but investigators who have closely examined the question have proposed that an optimal surgical delay may be 6–11 weeks [60, 67, 68], pointing to a potential shortcoming of conventional SCRT.

The Trans-Tasman Radiation Oncology Group (TROG) trial compared SCRT with LCRT and found that the two protocols differed mainly in the lower incidence of acute toxicity with SCRT and the superior rate of pCR for LCRT (15% vs 1%) [69, 70]. Both of these differences might tentatively be ascribed to the longer surgical delay with LCRT. The Stockholm III trial pursued this hypothesis by imposing a 4–8-week surgical delay on the Swedish SCRT protocol [60]. The pCR rate for SCRT with delay was 11.8% in a preliminary study [71] and 10.4% after a follow-up of 5.7 years [72]. This greatly exceeded the pCR of 0.3% for SCRT without delay and the pCR of 2.2% for conventional LCRT (the latter result, it should be noted, is atypically low). Tumor regression by the Dworak system and OS were also superior for SCRT with delay. Other studies have similarly modified SCRT and confirmed that tumor downstaging is enhanced [73–76]. A final observation, grounded in the economics of health care delivery, has considerable bearing on the controversy: the turn toward a capitation model may encourage a cost–benefit analysis that promotes future migration to SCRT [62].

Does tumor downstaging actually improve clinical outcomes? This is the critical question, but there is as yet no clear answer for it. Of note, the neoadjuvant rectal (NAR) score, designed to provide clinical trials with a reproducible short-term endpoint, has proven a useful tool precisely because it relies on the ability of downstaging to predict OS [77]. Greater downstaging is also known to improve the odds for sphincter preservation at surgery [42, 43], but in the last analysis, this can be true only if the change in rectal tumors has an impact on the behavior of surgeons. It should be added that treatment response is not reflected only in tumor

downstaging. Other measures, including reductions in tumor volume, may have greater prognostic significance. The key clinical relation—a link between preoperative tumor downstaging and oncologic outcomes—seems likely but has not yet been proven [78–82]. Nonetheless, the robust evidence that downstaging is susceptible to therapeutic manipulation and the very plausible hypothesis that oncologic benefit will follow have inspired the most important of all current trends in LARC treatment: the aggressive use of chemotherapy to achieve tumor regression and eradication of microscopic disease in the earliest phases of treatment.

Total Neoadjuvant Therapy (TNT)

Although the term total neoadjuvant therapy (TNT) refers to the delegation of all adjuvant therapy to the preoperative period [83], a literature review adhering to this definition would be unnecessarily limiting. Many studies hybridize TNT with adjuvant chemotherapy, while others, although inspired by the TNT model, leave the addition of adjuvant therapy to clinical discretion. Chemotherapy may be given before or after CRT ("induction" vs "consolidation"), and preoperative chemotherapy may be given with short-course RT, long-course CRT, or no RT at all. To these permutations can be added the chemotherapy protocol itself, which may employ a single agent or as many as four.

TNT is an evolving, but not a newly minted paradigm for the treatment of LARC. A regimen in which CRT was preceded by a course of 5-FU and mitomycin, and followed by chemotherapy postoperatively, was reported by Chau in 2003 [84]. It is unlikely, however, that exploration of the TNT paradigm would have proceeded in the accelerated fashion it has without advances in risk stratification. Using state-of-the-art pelvic MRI, and to a lesser degree, digital exam and endoluminal ultrasound [85], the MERCURY study [86, 87], among others [88], pioneered the effort to identify clinically important subgroups within the conventional TNM stages. Shown to be associated with low risk were (1) a tumor location > 10 cm from the anal verge; (2) an MRI showing no lymphovascular or lymph node invasion; and (3) a clinical estimate of a circumferential resection margin > 1 mm [68]. The capacity to identify patients at low risk provided an assurance that TNT would not subject large numbers of patients to overtreatment. Once low-risk patients and those with metastatic disease had been excluded, early intensified treatment offered the prospect of eradicating the micrometastases thought to produce distal relapses years later. The potential survival benefit was clear, and TNT was taken up by clinical investigators with considerable optimism and industry.

Phase II investigations of TNT were undertaken in earnest beginning about 2010. Most of these studies followed a protocol in which conventional CRT was preceded by induction chemotherapy, with pCR as the primary endpoint. Early work of this kind established a typical pCR rate of about 20% [89–91], even for operable, poor-risk rectal cancers. With modification of the chemotherapy protocol, including the introduction of FOLFOX, a pCR rate closer to 30% became more common [92]. The CONTRE study, for example, employed 8 cycles of FOLFOX and achieved a pCR of 33% [93]. The UK COPERNICUS trial [94, 95] was restricted to patients with evidence on MRI of venous invasion or infiltration of regional lymph nodes, raising the bar for success considerably. Using a TNT regimen of induction CAPOX (capecitabine/oxaliplatin) followed by SCRT and surgery, the investigators reported a 73% tumor response rate accompanied by minimal treatment-related toxicity and no treatment-related deaths.

The relation of treatment outcome to variations in the chemotherapy protocol was further examined in the prospective phase II TIMING trial [66, 96]. Patients with T2N0 rectal cancer received long-course CRT followed by 0, 2, 4, or 6 cycles of consolidation FOLFOX. The rate of pCR was 18% when no chemotherapy was given but rose to 38% with 6 FOLFOX cycles incorporated into a regimen which required surgery to be performed 20 weeks after CRT. The results are particularly valuable because they show that TNT protocols are able to achieve improvement in pCR rates without adding to the morbidity of surgery.

One stimulus for the contemporary proliferation of TNT studies is the option to combine components of RT and chemotherapy in different ways. A comparison of induction and consolidation chemotherapy was taken up by the German CAO/ARO/AIO-12 trial [97•]. Stage II–III patients with rectal cancer were randomly assigned to receive 3 cycles of FOLFOX either before or after CRT. Consolidation chemotherapy produced a pCR of 25%, significantly higher than the 15% rate for historical controls given preoperative CRT alone, and trending higher than the 17% rate for study patients who received induction chemotherapy ($p = 0.07$). The data for toxicity and patient compliance also favored consolidation chemotherapy.

The combination of TNT with a short-course radiation schedule was probed in the Polish II trial [98]. Patients with cT4 or fixed cT3 rectal cancer received SCRT followed by three cycles of consolidation FOLFOX. Oncologic outcomes for this group were compared with those for a group that was given long-course RT with concurrent 5-FU, leucovorin, and oxaliplatin but received no neoadjuvant chemotherapy before or after. Acute toxicity was less for patients receiving short-course TNT, and survival at 3 years was improved (73% vs 65%). The rate of margin-free resection, local control, and DFS, however, was the same for both groups. Moreover, at 8-year follow-up, the survival advantage associated with TNT/SCRT had vanished, and OS for both groups was 49%.

Many clinical outcome studies of TNT have compared it with conventional CRT. Cercek et al. [99] performed a retrospective analysis of 811 patients with T3/4 or node positive LARC, comparing induction FOLFOX followed by CRT and planned surgery with CRT followed by planned surgery and adjuvant chemotherapy. The combined clinical and pathologic response rate was 36% for TNT and 21% for patients receiving conventional CRT.

The phase II GCR-3 trial randomized 108 patients with LARC to receive either induction chemotherapy with 4 cycles of CAPOX followed by long-course CRT or standard CRT followed by surgery and chemotherapy [100, 101]. At 5 years, no difference was observed in rates of pCR (13–14%), local control, DFS, or OS. The rate of patient compliance, however, strongly favored TNT (94% vs 57%), reflecting the much lower incidence of serious treatment side effects in the TNT group (19% versus 54%). The multicenter Chinese STELLAR study [102] randomized patients to either SCRT followed by 4 cycles of consolidation CAPOX or long-course capecitabine-based CRT. Both groups received adjuvant CAPOX after TME. Despite a trend toward greater 3 + acute toxicity (17.6% vs 4.1%, $p = 0.07$), patients receiving TNT were more likely to complete treatment. A higher rate of pCR was also observed in the TNT-treated patients (26.2% vs 5.3%). Results of this kind are supported by the hypothesis that TNT may prevent distant relapses by allowing patients to receive the chemotherapy prescribed for them in full. This explains much of the clinical optimism TNT has engendered.

The phase III study PRODIGE 23 [103•] compared induction chemotherapy using FOLFIRINOX (6 cycles of oxaliplatin, leucovorin, irinotecan, and 5-FU) followed by long-course CRT with a regimen limited to long-course CRT. Both groups underwent TME and received adjuvant chemotherapy with FOLFOX or capecitabine, a departure from a strict neoadjuvant protocol. Patients in the induction chemotherapy arm were found to have a higher rate of pCR (27.5% vs 11.7%), a higher rate of 3-year DFS (75.7% vs 68.5%), and a higher rate of 3-year metastasis-free survival (78.8% vs 71.7%). While these outcomes support the hypothesis of early treatment sterilizing micrometastatic disease, it is important to remember that the intensity of therapy was altered here, not only the sequence.

RAPIDO [104•] was a phase III study that randomized 920 patients with T4 and N2 rectal cancer, and other markers of high risk, to SCRT followed by CAPOX/FOLFOX and surgery or to conventional capecitabine-based CRT followed by surgery. Postoperative chemotherapy was added to the CRT regimen at the discretion of participating hospitals. The regimen of SCRT with consolidation chemotherapy produced superior outcomes for pCR (27.7% vs 13.8%), 3-year local failure (8.7% vs 6.0%), and 3-year distant failure (19.8% vs 26.6%). Adjuvant chemotherapy was delivered to fewer than one-half of patients and did not appear on statistical analysis to bias the results.

A recent meta-analysis [105] reviewed seven studies representing over 1000 patients with LARC who were treated with TNT protocols. The results probably represent an accurate summary of the status of TNT to date. The rate of pCR for the pooled study population was 29.9% with a range of 17.2 to 38.5%—an outcome significantly better than the median pCR of 14.9% for the patients receiving conventional CRT. Data on DFS was available for only 3 of the studies examined, but the odds ratio of 2.07 favored TNT. Inconsistent reporting prohibited any determination of the effect of TNT on OS. A different survey, based on a large National Cancer Database cohort, reached an identical conclusion, albeit with a different emphasis: when OS for TNT was compared with that of conventional CRT, TNT was no worse [106].

Non-operative Management of LARC

In 2004, the Brazilian surgeon Angelita Habr-Gama, noting that 27% of her patients treated with CRT had no trace of rectal cancer after their initial chemoradiation, elected to hold their surgery indefinitely [107]. When a retrospective analysis was performed for those patients who had been placed in the non-operative treatment arm 4–5 years earlier, their incidence of DFS was found to be 92%. These results were illuminating in their own right, but they were received with heightened interest because they coincided with the growing imperative throughout the medical community to involve patients in clinical decisions, and to treat quality of life as a prioritized treatment outcome. The imperative to attend to the patient point-of-view remains an important consideration. A study, in 2020, asking patients with rectal cancer to list their treatment priorities found that they ranked first the avoidance of a permanent stoma—a striking result considering that the prevention of recurrent disease was ranked fourth [108].

Some clinicians expressed concern that Habr-Gama's results were unrepresentative and unreproducible, but many others set about trying to reproduce them. A retrospective report examined the result of withholding surgery from 32 patients who exhibited a complete clinical response (cCR) to RT and chemotherapy. Six of the patients suffered a local recurrence, but all were successfully treated with salvage surgery. After 2 years, OS for patients who had entered the watch and wait program was identical to that of patients who had received surgery at the outset [109].

The need to make more precise the meaning of a clinical "complete" response was addressed by a 2010 prospective study from the Netherlands [110]. Criteria for a cCR included no tumor mass on MRI, no rectal mass detectable

on physical exam, no evidence of fibrosis or ulceration on biopsy (if one was taken), and no suspicious lymph nodes. These criteria closely resemble those established by the more detailed and widely adopted Memorial Sloan Kettering Regression Schema [111]. The investigators followed 21 patients who had a cCR after a course of (non-TNT) chemoradiation. A 25-month follow-up period during which they underwent surveillance every 3 months determined that 20 of them remained recurrence-free.

The phase II OPRA trial [112•] assigned patients with LARC to 4 months of FOLFOX or CAPOX either before or after standard long-course CRT. Patients with a complete or near-complete response to neoadjuvant treatment were offered a watch-and-wait approach. At a median follow-up of 2.1 years, patient compliance with chemotherapy was similar for induction and consolidation TNT. DFS after 3 years did not differ for the two groups and did not surpass the historical control rate of 75%; however, the rate of long-term organ preservation for patients in the watch-and-wait arm was higher for the consolidation group (58% vs 43%) and surpassed historical controls in both groups.

Not every study has offered unqualified support for watch and wait. A retrospective study of 113 patients with LARC who had achieved a cCR reported that 82% of them were managed without a colostomy [113]. The rate of distant metastases was 36% for those requiring salvage surgery, but it is unclear if this illustrates the hazards of delaying surgery or simply the aggressiveness of one subgroup of cancers. A review of over 1000 patients in the watch-and-wait database provided data of particular value for clinicians who wish to create a surveillance protocol [114]. The incidence of local regrowth at 2 years was 25.3%, but increased very little thereafter; 96.7% of tumor regrowth was confined to the bowel wall and was therefore accessible to endoscopic and digital surveillance. Unsalvageable recurrences were rare. The import was that a surveillance program could be both effective and practicable. Another study of 129 patients who had entered a watch and wait program after achieving a cCR with conventional CRT reported a relatively high 34% rate of local recurrence; however, DFS and OS were no worse than for operated patients, and sphincter preservation at 3 years was superior [115].

TNT and Non-operative Management

Since cCR is the sine qua non for the watch and wait approach and the least disputed achievement of bimodality therapy (which we will refer to as TNT for convenience, even though treatment cannot be neoadjuvant without surgery), there are solid grounds for employing the two strategies in combination. Whether the rates of cCR with inclusion of a period of systemic therapy are superior to those of conventional preoperative CRT is less certain. Early studies reported rates for CRT to be as high as 78% [116], but experience has moderated that figure considerably. A 2019 study, for example, employing standard fluoropyrimidine-based chemoradiation for cT2-4N0-2 rectal cancer reported a cCR rate of 25% [117]. Turning to TNT, an impressive 1-year cCR rate of 68% was reported in a recent non-randomized prospective study employing SCRT with consolidation FOLFOX/CAPOX [118]. Patients in that study evaluated after 27.7 months without surgery had an OS of 100% with no evidence of residual disease or severe late toxicity. These highly favorable results must be generalized with caution, however. The study included only 19 patients, 21% of them with stage I disease. The rates of pCR reported in PRODIGE 23 and RAPIDO—27.5% and 27.7%, respectively—may be more representative of the levels clinicians can anticipate. An additional caveat is that uncertainty still attaches to the critical relation of both cCR and pCR to clinical outcome [119].

Conclusion: Where We Are Now

Do the studies reviewed above point to the next standard of care for LARC—a standard that can be defended as a replacement for conventional CRT with or without adjuvant chemotherapy? The question tends to obscure the sophistication of clinical decision-making in the modern era. Even the idea of a standard of care has now taken on a provisional quality it did not have in 1990, when the recommendation of the NIH Consensus Conference could be distilled to a single sentence. Whether or not it is standard in a formal sense, TNT is a well-established practice—and particularly so in the most influential and highly regarded treatment centers. The expert warning against its premature acceptance [83] is a clear sign that its acceptance has to some degree already occurred, and that guidelines are needed mainly to safeguard against its overuse. To heed this warning requires knowledge of risk. Indeed all of the current challenges to trimodal therapy—not only the nonsurgical management of patients receiving TNT but the options of chemotherapy without radiotherapy [120] and local excision in place of resection [121, 122]—are the product of an effort to match acceptable levels of toxicity to better predictors of individual risk.

The two outstanding risks to patients with LARC are disease recurrence, which poses a threat to survival, and sphincter loss or dysfunction, which poses a threat to quality of life. Based on the risk of recurrence, we recommend TNT for the majority of stage 2–3 rectal cancers, excluding rectal cancers extending no farther than the muscularis propria (T1-2). Patients staged T3 N0 are at relatively low risk for recurrence but are candidates for TNT if a distal location makes sphincter preservation unlikely. The preference for a TNT protocol over conventional CRT with

adjuvant chemotherapy is based on its high rates of cCR/pCR, low levels of toxicity, superior ability to deliver full-dose chemotherapy, and greater capacity to preserve quality of life.

The optimal TNT protocol has yet to be determined. LCRT and SCRT are both effective when used in combination with consolidation chemotherapy, which we generally prefer to induction chemotherapy based on its superior rate of cCR/pCR. Induction chemotherapy offers the potential advantage of earlier treatment of micrometastases and may be the preferred alternative in patients where the risk of distant recurrence is exceptionally high, a group which includes patients with tumors involving more than 3 lymph nodes (N2) and those demonstrating extramural vascular invasion. The optimal chemotherapy regimen for TNT protocols is the subject of intense investigation but is as yet unknown.

Current evidence supports the limited use of TNT combined with non-surgical management for patients who have demonstrated a cCR to neoadjuvant therapy and require either a permanent stoma or a very low anastomosis. This approach to watch-and-wait is justified by the very strong preference of patients for sphincter preservation and by the evidence that cCR, while an imperfect surrogate for pCR, predicts greater local control and DFS. The argument defending watch-and-wait for all patients who demonstrate a cCR after neoadjuvant therapy is not yet persuasive due to inconsistencies among studies in surveillance methods, treatment protocols, and definitions of cCR. When non-surgical management is elected, cCR must be confirmed by MRI, endoscopy, and digital exam at least 8 weeks after the end of treatment, and a scrupulous surveillance program must be in place. Enthusiasm for non-surgical management of LARC should not obscure the fact that residual microscopic disease will be undetected in patients with a cCR, and that both oncologic outcomes and quality of life are favorable for patients with LARC who have been treated with sphincter-preserving surgery.

Declarations

Conflict of Interest The authors declare no competing interests.
Human and Animal Rights and Informed Consent.
This article does not contain any studies with human or animal subjects performed by any of the authors.

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