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# Neoadjuvant Short- Vs. Long-Course Radiation for Locally Advanced Rectal Cancer: How to Choose

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## Opinion statement

Over the past decades, the treatment of locally advanced rectal cancer has evolved dramatically due to improvements in diagnostic imaging, surgical technique, and the addition of radiotherapy and/or chemotherapy. Fractionation of neoadjuvant radiotherapy with or without concurrent chemotherapy remains the subject of discussion and the question multiple recent trials have aimed to answer. In light of recent data and concern for locoregional recurrence, our institution favors long-course chemoradiation in most cases, especially in low-lying primaries, threatened circumferential resection margin, consideration of non-operative management, or if the surgeon has concerns for resectability. Exceptions would include cases of oligometastatic disease planned for metastasectomy in which curative-intent treatment was pursued or if additional factors required a reduction in treatment time.

## Introduction

Outcomes for patients with locally advanced rectal cancer (LARC) have significantly improved following innovations in surgical technique and the inclusion of radiotherapy (RT) and chemotherapy. With modern treatment regimens, 5-year survival rates are estimated at 67% [1]. In terms of radiotherapy

technique, optimal fractionation remains a topic of debate and the subject of recent trials. Here, we discuss the underlying data and rationale for utilization of short-course radiotherapy (SC-RT) versus long-course chemoradiation (LC-CRT).

## Treatment options

Historically, the management of LARC by surgical resection conferred suboptimal local control, often leading to local recurrences, substantial morbidity and mortality, and occasionally, salvage pelvic exenteration. The advent of total mesorectal excision (TME) did improve surgical disease control; however, local recurrence rates persisted at levels deemed clinically unacceptable without the integration of adjunct therapeutic modalities.

Since then, multiple large trials and accumulating evidence have established adjuvant RT as standard of care to improve local disease control in LARC [2]. The pivotal Swedish and Dutch trials demonstrated superior local control with the addition of neoadjuvant RT versus surgical monotherapy [3, 4]. Sequencing of RT was evaluated in the German Rectal Cancer Trial, a randomized controlled trial comparing preoperative versus postoperative chemoradiation [5]. Although no significant overall survival (OS) or disease-free survival (DFS) was shown, preoperative chemoradiation facilitated tumor downstaging, improved treatment adherence, decreased treatment-related toxicities, and reduced local recurrences. Preservation of tumor vasculature, enhanced tumor oxygenation, and more favorable preoperative anatomy may improve neoadjuvant chemoradiation efficacy.

The advent of SC-RT offered a viable alternative to conventional chemoradiation in which patients could be treated in just five fractions. First, the Polish Study compared 25 Gy/5fx followed by TME versus 50.4 Gy/28fx with concurrent chemotherapy followed by TME in patients with cT3-4 rectal cancer [6]. Despite study limitations including concerns with clinical staging, incomplete TME, and lack of post-operative chemotherapy, no difference was seen in sphincter preservation, the primary endpoint. Moreover, LC-CRT did not improve OS, local control (LC), or late toxicity. The TROG Intergroup Trial randomized patients with T3N0-2 rectal cancer to SC-RT followed by surgery and postoperative chemotherapy or LC-CRT followed by surgery and postoperative chemotherapy [7]. No difference was seen in local recurrence (LR), distant metastases, OS, or late toxicity; however, tumors within 5 cm of the anal verge trended toward higher LR (12.5%) in the SC-RT arm versus LC-CRT (3%, $p = 0.21$). A few years later, the Polish II Trial comparing SC-RT vs. LC-CRT in patients with fixed cT3 or cT4 rectal cancer was published. Initial 3-year results favored SC-RT with improved OS, pathological complete response (pCR), and acute toxicity; however, with long-term follow-up, SC-RT was no longer superior to LC-CRT in terms of OS, DFS, or late toxicity [8] (Table 1).

In the setting of neoadjuvant RT and surgical TME, the majority of recurrences occur distantly. Therefore, a total neoadjuvant therapy (TNT) approach was adopted in LARC to deliver RT and chemotherapy neoadjuvantly. Theoretical advantages include a favorable toxicity profile, improved compliance

**Table 1. Highlighted short-course versus long-course trials**

| Study name (Ref) | *n* | Median follow-up (months) | Clinical stage | Neoadjuvant treatment | Adjuvant treatment | pCR (%) | R0 resection (%) | Toxicity (Gr 3 + 4) | Other clinical outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Polish (Ref 6) | 312 | 48 | cT3-4 | A-RT (25 Gy)<br>B-CRT (50.4 Gy + 5FU/LV) | A-5FU/LV × 6 mo<br>B-5FU/LV × 4 mo | 1 vs. 16 | 87 vs. 96 | 10.1 vs. 7.1% | No difference in OS, DFS, LR, or severe late toxicity. Postop chemotherapy optional |
| TROG 01.04 (Ref 7) | 326 | 71 | cT3N0-2 | A-RT (25 Gy)<br>B-CRT (50.4 Gy + 5FU) | A-5FU/LV × 6<br>B-5FU/LV × 4 | 1 vs. 12 | 95 vs. 96 | 5.8 vs. 8.2% | No difference in LR, DM, or OS. NS increase in LR in distal primaries |
| Polish-II (Ref 8) | 515 | 84 | fixed cT3 or cT4 | A-RT (25 Gy)—> FOLFOX4<br>B-CRT (50.4 Gy + FOLFOX) | None | 16 vs. 12 | 77 vs. 71 | 10 vs. 8% | Initially reported OS benefit lost on f/u; no DFS, DM, LC |
| RAPIDO (Refs 15, 16) | 912 | 55 | cT4, extramural vascular invasion, cN2, involved mesorectal fascia, involved lateral LNs | A- RT (25 Gy)—> FOLFOX4 or CAPOX<br>B- CRT (50/50.4 Gy + Capecitabine) | A-None<br>B- optional FOLFOX (per institution) | 28 vs. 14 | 90 vs. 90 | 9 vs. 9–11% | Increased LRR with SC-RT. No difference in OS |
| STELLAR (Ref 17) | 599 | 35 | cT3-4 and/or cN + | A- RT (25 Gy)—>CAPOXx4<br>B- CRT (50.4 Gy + Capecitabine) | A-CAPOX × 2<br>B- CAPOX × 6 | 21.8 vs. 12.3 | 91.5 vs. 87.8 | Neoadj:26.5 vs. 12.6%<br>Adj: 3.3 vs. 11.8% | DFS and OS improved in RT arm; no differences in DM, LRR |

*Adj*: Adjuvant; *Cape* - Capecitabine; *CRT*- Chemoradiotherapy; *DFS* – Disease-Free Survival; *DM* – Distant Metastases; *LC* – Local Control; *LRR* – Locoregional Recurrence; *Neoadj* – Neoadjuvant; *OS* – Overall Survival; *pCR* – Pathologic Complete Response; *RT* – Radiotherapy; *SC-RT* – short course radiotherapy Table 1 – Highlighted Short Course versus Long Course Trials 9

of systemically dosed chemotherapy without delay, earlier ostomy reversal, and improved primary tumor downstaging with potential for organ preservation. Adopting a TNT approach also risks overtreatment of some patients, especially those who have not been accurately staged. This underscores the critical importance of meticulous patient selection and comprehensive preoperative imaging in situations where definitive surgical pathology will not be available [9].

Fluoropyrimidine-based chemotherapy serves as an effective means for enhancing systemic control while concurrently enhancing the radiosensitivity of primary rectal tumors. This approach has a noteworthy historical trajectory, with adjuvant chemotherapy demonstrating tangible improvements in recurrence and survival rates dating back to the 1980s, especially when integrated within treatment paradigms including radiotherapy [2].

The EORTC-22921 trial undertook a comprehensive evaluation of the incorporation of pre- or postoperative chemotherapy with neoadjuvant RT regimens. This investigation, however, failed to show a significant difference in OS or DFS, which could be partly attributed to suboptimal chemotherapy compliance and the utilization of outdated regimens and dosing protocols [10]. It is worth noting that while chemotherapy contributed to enhanced LC, not all patients underwent TME in this context.

More recently, chemotherapy strategies tailored for LARC, such as FOLFOX and CAPOX, have been derived from studies conducted on resectable colon cancer. These regimens, featuring the incorporation of oxaliplatin alongside adjuvant 5-FU, have yielded improved DFS outcomes, marking a notable advancement in the treatment landscape for LARC [11].

Numerous studies have diligently investigated the inclusion of neoadjuvant chemotherapy alongside neoadjuvant radiotherapy for LARC. Early data, both from single institutions and multi-institutional collaborations, provided substantial support for the feasibility and efficacy of TNT in this clinical setting [12].

The phase 2 Spanish GCR-3 trial, which compared neoadjuvant to adjuvant CAPOX in conjunction with chemoradiation and TME, yielded promising results. Notably, it showcased enhanced therapy compliance and a favorable acute toxicity profile in favor of the TNT approach [13]. Additionally, the PRODIGE-23 trial demonstrated an improved DFS when induction FOLFIRINOX was incorporated into the chemoradiation/TME/chemotherapy regimen [14]. This improvement was primarily attributed to a reduction in DM and an increase in pCR rates, potentially stemming from intensified chemotherapy, increased chemotherapy cycles, or modifications in therapy sequencing.

Simultaneously, a noteworthy development emerged with the advent of 5-fraction SC-RT as a viable alternative to conventional chemoradiation within TNT protocols. Building on the Polish-II paradigm, the RAPIDO trial for high-risk LARC compared SC-RT/chemotherapy/TME versus chemoradiation/TME/optional chemotherapy. This SC-RT TNT approach initially demonstrated a lower incidence of locoregional failure at three years (23.7% vs. 30.4%) and markedly improved pCR rates (28% vs. 14%) [15•]. However, at a median follow-up of 5.6 years, LRR was more common in the SC-RT group (10% vs. 6%, $p = 0.027$) as well as a breached mesorectum (21% vs. 4%,

$p = 0.048$). The study also identified enlarged lateral lymph nodes, positive circumferential resection margin, tumor deposits, and pathologically positive lymph nodes as significant predictors for LRR [16••]. Similarly, the STELLAR trial conducted a comparative assessment between a SC-RT TNT regimen and neoadjuvant chemoradiation followed by adjuvant chemotherapy. The SC-RT TNT regimen exhibited favorable 3-year DFS and OS rates, potentially influenced by decreased chemotherapy compliance in the chemoradiation arm (Table 1). Long-term follow-up data is anticipated [17].

In exceptional responders, non-operative management (NOM) approaches are being explored. Despite achieving effective tumor control, trimodality treatment for LARC confers high rates of morbidity in terms of bowel, urinary, and sexual side effects which can permanently impair survivors' quality of life. Moreover, distal tumors can be particularly challenging and result in permanent colostomy [18]. Early NOM data reported a clinical complete response (cCR) rate of 49% with CRT alone, with 31% of these cases eventually developing local recurrence [19]. With the adoption of TNT approaches, retrospective institutional data suggested improved NOM candidacy with the addition of systemically-dosed chemotherapy [20]. The OPRA study, a randomized controlled trial evaluating sequencing of chemotherapy (induction versus consolidation) with CRT in a TNT approach, offered NOM to patients with cCR. Similar 3-year DFS compared to historical trimodality controls were seen. Importantly, consolidative chemotherapy sequencing showed favorable 3-year TME-free survival compared to induction sequencing [21••]. Similar improvement in pCR rates were associated with CRT/consolidative chemotherapy TNT sequencing in the CAO/ARO/AIO-12 study [22].

The shifting treatment paradigm for LARC has conferred significant improvements in outcomes; however, debate remains regarding the optimal radiation technique. Treatment selection is multifactorial and often relies on discussion between treating physicians and the patient. With continued innovation and refinement of patient selection, response-adjusted therapy, and personalized treatment approaches, the future of LARC treatment is encouraging.

## Declarations

**Author contributions**
C.W. conceptualized the article and critically revised the work. S.A. performed the literature search, wrote the main manuscript text, and prepared the table.

## Compliance with Ethical Standards

**Competing Interests**
The authors declare no competing interests.

**Human and Animal Rights**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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