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Tailored Approaches and Patient-centered Care: The Current Landscape of Neoadjuvant Therapy in Rectal Cancer

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Introduction

Colorectal cancer (CRC) is the third most diagnosed cancer in Canada and worldwide.[1] Although mortality rates have declined, it remains the second most lethal malignancy worldwide.

For patients with locally advanced rectal cancer (LARC), several new concepts have been introduced in recent years for treatment sequencing and de-escalation. The use of pelvic magnetic resonance imaging (MRI) for initial staging and neoadjuvant therapy response assessment has become a key part of the workup for LARC, utilizing the expertise of specialist radiologists. High-volume rectal cancer centers have adopted total neoadjuvant therapy (TNT) as a preferred approach for many patients with LARC. There is rising interest in shortening the duration of chemotherapy or radiation, or even omitting radiation altogether for select patients, to reduce the burden of long-term toxicities. For patients who achieve clinical complete or near-complete responses (cCR or nCR) to neoadjuvant therapies, nonoperative management (NOM) has emerged as an option to avoid the complications of a total mesorectal excision (TME).

This paradigm shift has resulted in numerous treatment options for many patients with rectal cancer, enabling a more individualized, multidisciplinary approach to care.[2] Clinicians must understand how to interpret the evidence around these new concepts to successfully implement them into clinical practice. This review summarizes the recent evidence for neoadjuvant therapy approaches in rectal cancer to provide a context for this paradigm shift to a tailored therapeutic strategy.

Total Neoadjuvant Therapy

Neoadjuvant chemoradiation is the established standard of care for patients with Stage II and III rectal cancer since the results of the German Rectal Cancer Study 20 years ago.[3] However, more recently, there has been a growing interest in moving systemic chemotherapy earlier in the treatment sequence, resulting in the concept

of TNT, whereby all chemotherapy is delivered prior to surgery.

The potential benefits of this shift in treatment sequencing can be divided into those impacting efficacy, safety, and treatment adherence. Evidence from multiple trials shows that TNT results in improved oncologic outcomes compared to standard chemoradiation alone. In the PRODIGE-23 trial, modified oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil (FOLFIRINOX) before preoperative chemoradiation was compared to standard preoperative chemoradiation with adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX).[4] The updated results showed a disease-free survival (DFS) and overall survival (OS) benefit at seven years for the TNT arm.[5] The RAPIDO trial used a slightly different experimental arm of short-course radiation followed by three months of FOLFOX prior to surgery, compared to long-course chemoradiation followed by surgery and optional adjuvant chemotherapy.[6] The most recent results of this trial showed a sustained benefit in the TNT arm for disease-related treatment failure. In this trial, no difference in OS was observed between the two arms, and interestingly, there was a higher rate of locoregional recurrence in the TNT arm compared to long-course chemoradiation.[7] The Phase III TNTCRT trial also differed slightly in its experimental arm, comparing capecitabine and oxaliplatin (CAPOX) TNT to standard long-course chemoradiation and adjuvant chemotherapy **(Table 1)**. This study also showed a significant improvement in DFS for the TNT arm but no difference in OS.[8]

Concerning safety and treatment adherence, multiple studies have shown similar or reduced rates of serious toxicity with a TNT approach.[4,6,8,9] Surgical risk and complication rates do not appear to be significantly worsened with the shift to preoperative chemotherapy compared to standard adjuvant chemotherapy, even with the use of FOLFIRINOX in the PRODIGE-23 trial.[4]

Patient selection is critical to ensure that maximal benefit from TNT is achieved, over-treatment of patients with lower-stage disease is minimized, and unnecessary chemotherapy-related complications are avoided. Where possible, cases should be reviewed in a multidisciplinary tumour board. The specific inclusion criteria for TNT differ between the current trials. For example, in the PRODIGE-23 trial, patients with cT3 or cT4 disease were included. However, the RAPIDO and TNT CRT trials included a more high-risk cohort, including those with cT4a or cT4b tumors, who were extramural vascular invasion (EMVI) positive, in which the mesorectal fascia was involved, or those with a higher nodal burden (cN2 or enlarged lateral nodes).[4,6] Generally speaking, patients should have Stage 3 disease and/or higher-risk features to have maximal benefit from this treatment intensification.

Radiation-sparing Approach

The avoidance of radiation has emerged as a potential option for select patients, with a key driver being the prevention of long-term radiation toxicity. Recent evidence comes from the PROSPECT study, a randomized non-inferiority trial in patients with early- or intermediate-advanced upper and mid rectal cancers.[10] Patients received either standard long-course chemoradiation or three months of FOLFOX with select use of chemoradiation (in cases with <20% tumor response or <5 cycles received due to toxicity) prior to surgery, which is then followed by adjuvant chemotherapy. Only 9% of patients in the experimental arm ultimately required neoadjuvant chemoradiation. The trial met its primary endpoint, confirming the non-inferiority of FOLFOX with selective chemoradiation. Notably, at twelve months after treatment, patients in the experimental arm reported less bowel, bladder, and sexual dysfunction compared to those in the standard chemoradiation arm.

Avoiding radiation has emerged as a useful option for specific patient subgroups, such as young women hoping to preserve fertility. Patient selection is again important, as the PROSPECT study excluded patients with T4 and N2 disease and those with low rectal cancers. Potential future approaches include the expansion of radiation avoidance to patients with early-stage rectal cancers. For example, the currently recruiting Neo-RT trial will explore the role of minimally invasive surgery after neoadjuvant FOLFOX and selective radiation in patients with T1 and T2 rectal cancers.[11]

Neoadjuvant Immune Checkpoint Inhibitor Therapy for Mismatch Repair-deficient Rectal Cancer

Up to 10% of rectal cancers may carry a germline or somatic deficiency in DNA mismatch repair (dMMR) and are less responsive to fluoropyrimidine-based chemotherapy.[12,13] For patients with dMMR advanced CRC, the

Author	Year	Common name	Format	Patients	Clinical stage included	Mandatory TME	Landmark follow-up (years)	Study arms	DFS	OS	pCR (%)
MMR proficient											
Conroy *et al.*[4,5]	2021, 2023	PRODIGE-23	Phase III RCT	461	T3-4	Yes	7	3 mos FOLFIRINOX then LCCRT prior to TME, then 3 mos ACT CRT prior to TME, then 6 mos ACT	66.2% vs. 60.4% [S]	76.3% vs. 71.9% [S]	28% vs. 12% [S]
Bahadoer *et al.*[6,7]	2021	RAPIDO	Phase III RCT	912	At least 1 of: T4a/b, EMVI, N2, involved MRF or lateral LNs	Yes	5	SCRT then 3 mos CAPOX or FOLFOX, prior to TME LCCRT prior to TME, then 4 mos ACT	DrTF 27.8% vs. 34% [S]	81.7% vs. 80.2% [NS]	28% vs. 14% [S]
Wang *et al.*[8]	2024	TNTCRT	Phase III RCT	458	T4, N2, T3c-d with EMVI, threatened MRF	Yes	3	1 cycle CAPOX then 2 cycles CAPOX with concurrent RT, then further 3 cycles CAPOX, prior to TME LCCRT prior to TME, then ACT	76.8% vs. 67.9% [S]	89.8% vs. 88.2% [NS]	27.5% vs. 9.8% [S]
Schrag *et al.*[10]	2023	PROSPECT	Phase III randomized noninferiority	1128	T2N1, T3N0 or T3N1	Yes (sphincter-sparing surgery)	5	3 mos FOLFOX then selective LCCRT prior to TME, option of ACT LCCRT prior to TME, option of ACT	80.8% vs. 78.6%	89.5% vs. 90.2%	21.9% vs. 24.3%

Author	Year	Common name	Format	Patients	Clinical stage included	Mandatory TME	Landmark follow-up (years)	Study arms	DFS	OS	pCR (%)
Verheij *et al.*[19,20]	2024	OPRA	Phase II randomized trial	324	T3-4N0 or N1-2	No	5	INCT-CRT prior to TME or NOM CRT-CNCT prior to TME or NOM	71% and 69%	88% and 85%	TME-free survival 39% and 54%
MMR-deficient											
Cercek *et al.*[15,16]	2022, 2024	Dostarlimab study	Phase II	42	II and III	No	1.5	6 mos dostarlimab then NOM if cCR, or CRT and TME if residual disease	100%	100%	cCR 100%
Chen *et al.*[17]	2023	Sintilimab study	Phase II	16	T3-4 or N+	No	1.5	8 cycles sintilimab before TME or NOM, or 4 cycles sintilimab before TME then 4 cycles adjuvant sintilimab +/- CAPOX	100%	100%	cCR 75%

Table 1. Recent key trials for neoadjuvant therapy in rectal cancer; *courtesy of Tharani Krishnan, MD*
Abbreviations: ACT: adjuvant chemotherapy; **CAPOX:** capecitabine plus oxaliplatin; **cCR:** clinical complete response; **CRT:** chemoradiotherapy; **CRT-CNCT:** chemoradiotherapy followed by consolidation chemotherapy; **DFS:** disease-free survival; **DrTF:** disease-related treatment failure; **EMVI:** extramural vascular invasion; **FOLFIRINOX:** folinic acid, fluorouracil, irinotecan, and oxaliplatin; **FOLFOX:** folinic acid, fluorouracil, and oxaliplatin; **INCT-CRT:** induction chemotherapy followed by chemoradiation; **LCCRT:** long-course chemoradiotherapy; **LNs:** lymph nodes; **MMR:** mismatch repair; **mos:** months; **MRF:** mesorectal fascia; **NOM:** nonoperative management; **OS:** overall survival; **pCR:** pathological complete response; **RCT:** randomized controlled trial; **RT:** radiotherapy; **SCRT:** short-course radiotherapy; **TME:** total mesorectal excision; **vs.:** versus; **[NS]:** not significant; **[S]:** significant.

established standard-of-care first-line treatment is the immune checkpoint inhibitor (ICI) pembrolizumab.[14]

Several prospective studies in patients with early-stage dMMR CRC have recently demonstrated robust responses to ICIs. For patients with dMMR LARC specifically, 6-month treatment with dostarlimab achieved a cCR rate of 100% in a single-arm Phase II study including 42 patients.[15,16] With a median follow-up of 17 months, no patients have required chemoradiation or surgery. Another Phase II study of neoadjuvant sintilimab given for 12 to 24 weeks resulted in a cCR in 12 out of 15 patients.[17] While promising and likely to change practice, larger studies with longer follow-up are awaited to confirm the sustained benefit of neoadjuvant ICIs. Several unanswered questions remain, such as the optimal duration of treatment, the need for combination ICI treatment, and the role of NOM for sustained cure after ICIs. Access to this treatment outside of a clinical trial setting remains an issue in Canada, with ICIs only approved in the first-line dMMR metastatic setting.

Nonoperative Management

Patients with rectal cancer are increasingly interested in pursuing NOM. The purpose of omitting surgery is primarily to allow for organ preservation and minimize the risk of late complications, including urinary incontinence and bowel and sexual dysfunction. This is particularly important for patients with low rectal cancers, who often wish to avoid the permanent ostomy associated with an abdominoperineal resection (APR). In fact, a survey of patients in Canada found that patients would accept a 20% absolute decrease in survival with NOM relative to APR, while physicians would only accept a 5% survival reduction.[18]

While the NOM approach was initially reported for patients who achieved a cCR after chemoradiation alone, TNT has enabled maximal downstaging, and may allow for NOM in up to half of patients with LARC. In a prospective Phase II study, increasing the duration of chemotherapy from zero to three months after chemoradiation resulted in higher pathologic complete response (pCR) rates (18%-38%).[9] Additionally, an intermediate group of patients who achieve nCR after TNT may also benefit from NOM.

In the randomized Phase II OPRA trial, patients received either chemoradiation followed by four months of consolidation chemotherapy (CNCT) or chemoradiation after induction chemotherapy (INCT). Those who achieved a cCR or nCR were offered NOM; otherwise, TME was recommended. 5-year DFS rates were similar between the two arms.[19] However, TME-free survival was 54% in the CNCT arm and 39% in the INCT arm. For those with tumor re-growth, 94% occurred within the first two years. DFS was similar for patients who underwent TME after neoadjuvant therapy and TME after re-growth. The updated analysis shows organ preservation in approximately half of the patients, with higher rates (77%) in those with a cCR compared to nCR (40%).[20]

Accurately assessing clinical tumor response after neoadjuvant therapy is paramount to selecting patients for NOM. In the OPRA trial, patients had biopsy-proven rectal adenocarcinoma, and were staged with pelvic MRI, a full colonoscopy, and computed tomography (CT) of the chest, abdomen, and pelvis. Re-assessment occurred at 8 ± 4 weeks after completion of neoadjuvant therapy, and included digital rectal examination, endoscopy, and MRI. At the initial consultation, baseline features associated with lower cCR rates should be considered, such as tumor <1 mm from the circumferential resection margin, EMVI, and extensive mesorectal/pelvic nodal involvement. In addition, limitations exist with regard to accurately distinguishing post-radiation changes from residual disease and may add complexity to the decision of whether to offer NOM to a patient.

NOM should be undertaken in high-volume centers with experienced MRI radiologists and colorectal surgeons, and ideally in the context of a clinical trial or standardized protocol. Ongoing trials are investigating the optimal algorithms of TNT delivery and response assessment to further expand the number of patients who may benefit from NOM.

Conclusion

The neoadjuvant approach to rectal cancer is an evolving area. Results of several clinical trials in recent years have led to a paradigm shift towards tailoring an individualized treatment sequence that aligns with the patient's goals. Improvements in systemic therapy options, radiation delivery, and surgical expertise can potentially spare patients from adverse long-term treatment sequelae, while maintaining oncologic outcomes. A concerted

multidisciplinary approach should be considered mandatory for developing appropriate patient-centered strategies for patients with LARC.

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