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Management of rectal cancer in the era of total neoadjuvant therapy and watch and wait: A multidisciplinary team discussion at the Australasian Gastro-Intestinal Trials Group (AGITG) Annual Scientific Meeting 2022

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Abstract

Rectal cancer is a common malignancy. The management of rectal cancer has recently evolved and has undergone a paradigm shift with the advent of treatment approaches such as total neoadjuvant therapy and the watch-and-wait approach. However, despite the recently available evidence, there is no consensus on the optimal management approach in the setting of locally advanced rectal cancer. To address some of the controversies, a joint multidisciplinary panel discussion was conducted at the Australasian Gastro-Intestinal Trials Group (AGITG) Annual Scientific Meeting in November 2022. Members from different subspecialties formed two panels and discussed three clinical cases in a debate format. Each case represented some of the complex issues faced by clinicians in this setting. The discussion is now presented in this manuscript, which

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depicts the different available management approaches and reiterates the importance of a multidisciplinary approach.

KEYWORDS
rectal cancer, total neoadjuvant therapy, watch and wait

1 | INTRODUCTION

Colorectal cancer is the third most common malignancy worldwide, with one third of cases occurring in the rectum. In nonmetastatic rectal cancer, local recurrence rates are higher than in colon cancer. However, developments in staging techniques, improvements in surgical management (such as total mesorectal excision [TME] and optimal surgery for lower rectal cancer), and selective use of additional treatments, including radiotherapy and chemotherapy, have led to improvements in survival and reduction in the rate of local recurrence in rectal cancer.[1]

Total neoadjuvant therapy (TNT) involves the sequential administration of doublet or triplet combination chemotherapy in addition to preoperative (chemo-)radiation. The recent publication of three prospective randomized trials led to the inclusion of TNT regimens as an evidence-based approach in guidelines on the management of rectal cancer. In the RAPIDO study, patients with locally advanced rectal cancer with any one of the high-risk features (including T4 disease, extramural vascular invasion [EMVI], involvement of mesorectal fascia, threatened circumferential resection margin [CRM], N2 disease, and involvement of lateral nodes) were randomized to short-course radiation followed by consolidation chemotherapy with FOLFOX/CAPOX for 18 weeks versus standard long-course chemoradiation (CRT) followed by optional adjuvant FOLFOX/CAPOX for 24 weeks. The experimental arm had doubled the pathological complete response (pCR) rates compared to the standard arm (28% vs. 14%, $p < 0.001$) and lower disease-related treatment failure at 3 years (23.7% vs. 30.4%, respectively).[2]

The second trial, PRODIGE 23, randomized patients to either 3 months of triplet FOLFIRINOX chemotherapy followed by long-course CRT or standard long-course CRT. Both arms received additional adjuvant FOLFOX (for 3 months in the experimental arm and 6 months in the control arm). The experimental arm again achieved higher pCR rates (28% vs. 12%, $p < 0.001$) and 3-year disease-free survival (DFS) (76% vs. 69%, $p < 0.05$) than the standard arm, respectively.[3]

The third trial, OPRA, randomized patients with stage II or III rectal adenocarcinoma to 4 months of FOLFOX/CAPOX given either before (induction arm) or after (consolidation arm) long-course CRT. The trial design compared 3-year DFS in each arm to a 75% historical rate, but not between arms. However, at 3 years, although there was no difference between the arms in DFS, distant metastases-free survival, local recurrence rates or overall survival (OS), the consolidation arm achieved 3-year TME-free survival of 53% versus 41% in the induction arm.[4] Table 1 summarizes the results of these three trials and includes the results of the randomized phase 2 CAO/ARO/AIO-12 trial, which provided the first evidence for the role of consolidation therapy in a TNT approach for rectal cancer.[5]

However, despite this recent randomized trial evidence, there is no consensus on the optimal management approach in this setting. Some of the controversies that still exist include the evolving role of imaging, the use of TNT versus upfront surgery in early low rectal cancers, the type of radiation used (short-course radiation vs. long-course CRT), the order of chemotherapy and radiation (induction vs. consolidation chemotherapy), and the use of a nonoperative approach ("watchful waiting") in patients who achieve a clinical complete (or near-complete) tumor response after induction chemotherapy followed by long-course CRT, or after short-course radiation and consolidation chemotherapy.

To address some of these issues, a joint multidisciplinary panel discussion was conducted at the annual Australasian Gastro-Intestinal Trials Group (AGITG) Annual Scientific Meeting on 15 November 2022. Members from different subspecialties formed two panels and discussed three clinical cases in a debate format (TG: colorectal surgeon, EK: radiation oncologist, and MJ: medical oncologist in panel A; and TS: colorectal surgeon, AO: radiation oncologist, and ES: medical oncologist in panel B). KG: expert radiologist discussed the role of magnetic resonance imaging (MRI) in rectal cancer and reviewed the imaging. SV and AJ: both medical oncologists moderated the discussion. The meeting was attended by medical oncologists, colorectal surgeons, radiation oncologists, radiologists, nurses, research scientists, clinical trial staff, and consumer representatives.

2 | THE EVOLVING ROLE OF IMAGING IN THE MANAGEMENT OF RECTAL CANCER

2.1 | Features of a good quality scan and report

Accurate staging on MRI requires a high-resolution T2 (HRT2) sequence as defined by the MERCURY protocol.[6] This defines a 3 mm slice thickness, voxel size of 1.1 mm^3 using four signal averages (number of signal averages [NSA]). In 2002, the HRT2-weighted MRI sequence took >6 min to acquire, and although newer magnets can achieve the same results in 3–4 min, sites should ensure they are taking the time required. Faster scans with lower resolution reduce the ability to differentiate adjacent tissues in small areas. It is also possible to achieve higher resolution, for example, in early tumors, by using 2 mm slices with five NSA in a focused area.

As each HRT2 sequence takes time with limited coverage, it is useful if the surgeon gives an indication of the height of the lesion or resected

TABLE 1 Randomized controlled trials addressing the role of total neoadjuvant therapy in rectal cancer.

Trial arm	Inclusion criteria	Arm	Sequence of therapy in each arm			Adjuvant chemotherapy in the experimental arm	Results experimental vs. control Follow-up results (at 3 and 5 yrs)
RAPIDO phase III open-label RCT *N* = 920	A pelvic MRI with at least one of the risk factors T4a, EMVI, N2, MRF+, involved lateral lymph nodes	Experimental	SCRT (1 wk)	Chemotherapy 6xCAPOX (18 wks) or 9xFOLFOX4 (18 wks) starting with 11–14 days of completion of SCRT	Surgery TME 2–4 wk post chemotherapy	No further adjuvant chemotherapy	pCR 27.7% vs. 13.8% DrTF 23.7% vs. 30.4% DM 20% vs. 26.8% LR 8.3% vs. 6% Updated 5 yr data: LR 12% vs. 8% Predictors of local recurrence: enlarged lateral lymph nodes, positive CRM, tumor deposits, and node positivity at surgery were predictors of local recurrence
		Control	LCCRT (5 wks) with capecitabine	Surgery (8–12 wks post-RT)	Chemotherapy 8xCAPOX 12xFOLFOX4		
PRODIGE 23 phase III open-label RCT *N* = 461	cT3/T4, M0, <15 cm from verge	Experimental	Chemotherapy 6xmFOLFIRINOX (12 wks)	LCCRT (5 wks), started 1–3 wk post-NACT	Surgery	Chemotherapy 3 months (6 cycles of modified FOLFOX or 4 cycles of capecitabine	pCR 26.6% vs. 19.8% DFS 75.7% vs. 68.5% MFS 78.8% vs. 71.7% 3yOS 90.8% vs. 87.7%
		Control	LCCRT (5 wks + capecitabine	Surgery (8–12 wk post-RT)	Chemotherapy (6 months FOLFOX or capecitabine)		
							Results at 3 yrs
OPRA phase II RCT *N* = 324	Stages II and III	Experimental "induction"	Chemotherapy FOLFOX or CAPOX (16 wks)	LCCRT (5 wks) 5FU or capecitabine	Restage 8–12 wks followed by surgery or watch and wait	No further adjuvant chemotherapy	DFS 76% vs. 76% NS DMFS 84% vs. 82% NS OP 41% vs. 53% (*p* 0.01)
		Control "consolidation"	LCCRT (5 wks) + 5FU or capecitabine	Chemotherapy FOLFOX or CAPEOX (16 wks)	Restage 8–12 wks surgery or watch and wait		
AIO-12 phase II RCT *N* = 311	cT3 tumor less than 6 cm from anal verge, cT3 tumor of middle third of rectum with extramural spread into the mesorectal fat by 5 mm (>T3b), cT4 tumors, or LN involvement on MRI	Induction arm	Chemotherapy 3 cycles of FOLFOX (6 wks)	LCCRT with 5FU and oxaliplatin	Surgery after 18 wks from initiation of treatment	No adjuvant therapy was recommended	Induction vs. consolidation pCR 17% vs. 25% DFS 73% vs. 73% LRR 6% vs. 5%
		Consolidation arm	LCCRT with 5FU and oxaliplatin	Chemotherapy with three cycles of FOLFOX			

Abbreviations: CRM, circumferential resection margin; DM, distant metastases; DrTF, disease-related treatment failure; EMVI, extramural venous invasion; LCCRT, long-course chemoradiation therapy; LN, lymph nodes; LR, local recurrence; MFS, metastases free survival; MRF, mesorectal fascia; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; OP, organ preservation; OS, overall survival; pCR, pathological complete response; RCT, randomized controlled trial; SCRT, short-course radiation therapy; TME, total mesorectal excision; wks, weeks; yrs, years.

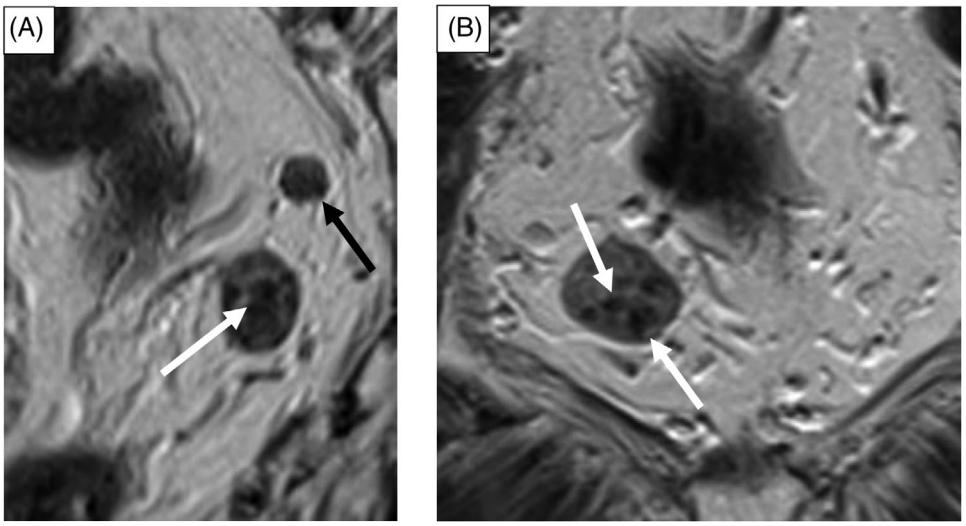

FIGURE 1 (A and B) **Morphological criteria for calling lymph nodes malignant on magnetic resonance imaging (MRI)**. These include an irregular outline (black arrow) corresponding to extracapsular spread and internal heterogeneity (white arrow) corresponding to intranodal tumor deposits. The features may be present singly or combined but should be confirmed on two high-resolution T2 planes. Visible on (a) sagittal and (b) coronal oblique.

tumor to ensure appropriate coverage, as this may not be obvious on MRI.

Using a template increases report completeness, and a radiologist reporting rectal MRI should feel confident to report on all items. A suggested template is included in the Australian Colorectal Cancer Clinical Guidelines.[7]

2.2 | Important imaging findings

The mrT stage matches well with pathology, particularly the distance of spread beyond the muscularis. The most challenging areas on MRI are the differentiation between deep T1 versus early T2 and full thickness T2 versus T3a (<1 mm spread).[8] Given prognostic similarities between these latter groups in many countries, this does not have significant clinical implications.[1]

The ability of MRI to detect malignant lymph nodes (LN) has been debated over the years. The highest accuracy is achieved using morphological criteria on HRT2 scans using the MERCURY protocol. The irregular outline corresponds to extracapsular spread, and internal heterogeneity reflects intranodal tumor deposits (TD) (Figure 1). As the HRT2 slice thickness is 3 mm, nodes <3 mm cannot be adequately assessed. Using size does not increase accuracy as most malignant LNs are small, and some large LNs are benign.[9,10]

Over the last decade, there has been increasing recognition of the presence of both LN and non-nodal TD in the mesorectum; the latter are categorized as N1c in AJCC eighth edition.[11] TDs have been shown to have much greater prognostic significance than LNs,[12,13] so historical outcome data using the Tumor, Node, Metastasis (TNM) classification is misleading, as it combines LNs and TDs, which have different prognostic implications. TDs are easier to identify on imaging as they are irregular nodules closely associated with veins (Figure 2). Even small TDs are found when following the veins from the tumor site and may spread superiorly or laterally. Due to this visible association with veins on multi-planar imaging, they are often reported as discontinuous EMVI by radiologists. This can be more difficult for pathologists, who review discrete sections and may not appreciate the relationship to a vein. The definition of N1c in the eighth edition is problematic and is hoped to be changed in the next edition.[14] The ability to detect and report TDs is still developing in some radiologists, but their identification should be encouraged and understood by clinicians.

Lateral LN involvement has a proposed size cutoff of 6–7 mm,[15] but a smaller node that is clearly irregular and/or heterogeneous should also be considered suspicious.[16]

2.3 | The role of MRI in follow-up assessment

MRI is increasingly used in the follow-up assessment. The recommended posttreatment MRI report in Australia stages any residual tumor and fibrosis and provides an MRI tumor regression grade (mrTRG) score.[7] mrTRG describes the relative proportions of tumor and fibrotic signal, noting all residual mesorectal disease contributes to the score, including malignant LN and TDs. As low T2 signal fibrosis may contain tumor cells, the ymrT stage and CRM involvement describe the maximum extent of the tumor and nodular fibrosis (not thin strands of trogdesmoplasia) (Figure 3), so a case with only fibrotic signal (mrTRG 2) may still be ymrT3d, CRM positive. A vessel that has returned to normal signal is considered EMVI negative, even if thickened.[17] There is no consensus on the optimal staging of LN and TDs posttreatment, but a cutoff >2.5 mm has an area under the receiver operating characteristic curve of .78 for the prediction of residual LN metastases.[18] A node that remains irregular should be considered suspicious.

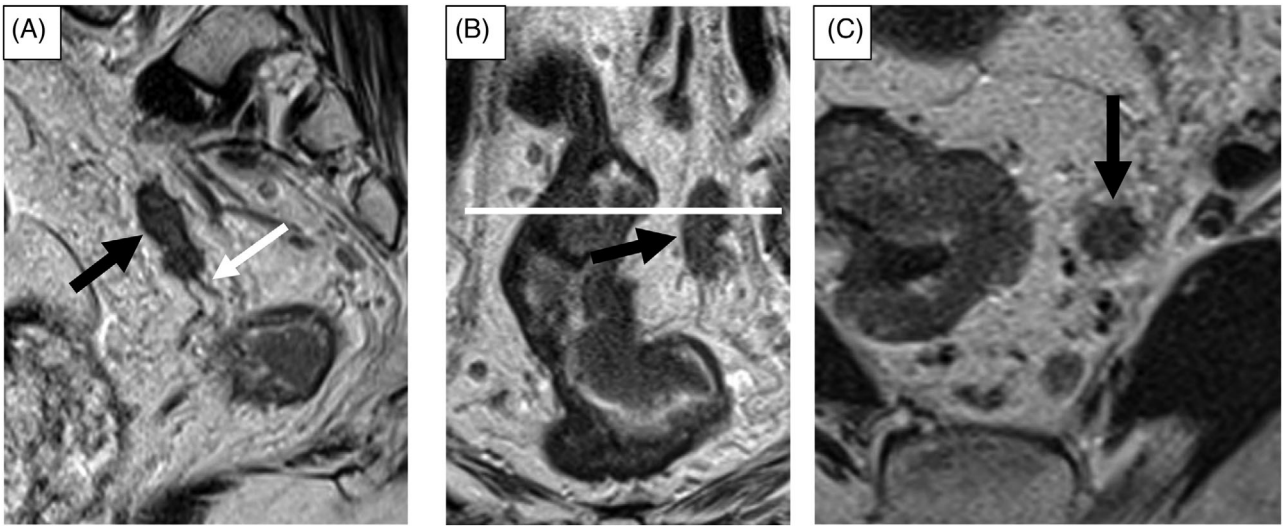

FIGURE 2 (A and B) **This elongated mesorectal tumor deposit (black arrow) is clearly associated with veins (white arrows) on (a) sagittal and (b) coronal magnetic resonance imaging (MRI) images**. However, when assessed in the axial plane only (c) as in pathology, it can easily be mistaken for a totally replaced lymph node. The axial slice position (white line) is shown on the coronal image.

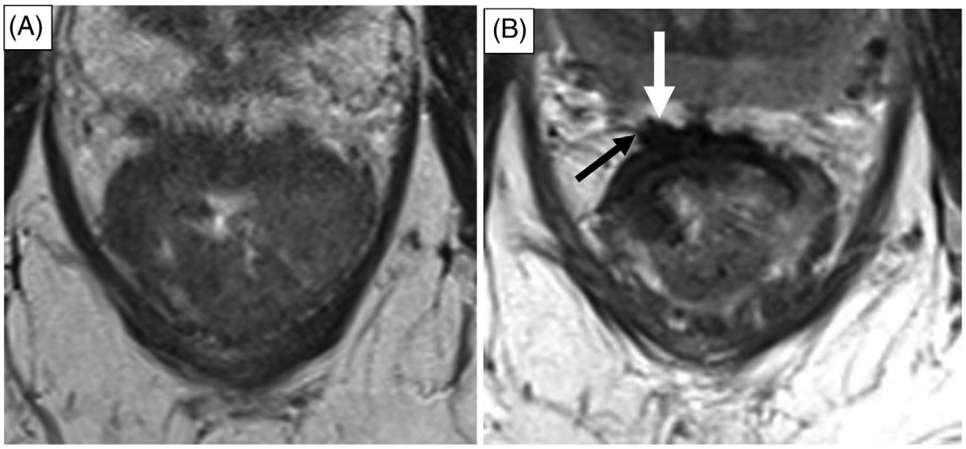

FIGURE 3 **(A) Pretreatment and (B) posttreatment axial HRT2 images of a low rectal tumor**. Pretreatment stage mrT3b, extramural vascular invasion (EMVI) positive, circumferential resection margin (CRM) involved. Posttreatment, there is only low T2 signal fibrosis, with no visible tumor signal consistent with mrTRG 2. However, the low T2 signal continues to breach the muscularis by 4 mm (white arrow) and touches the mesorectal fascia (black arrow). As it is not possible to know if there are residual microscopic tumor cells, MRI stages any residual tumor and fibrotic signal. So, the posttreatment report is mrTRG2, ymrT3b, ymrEMVI negative, and ymrCRM involved.

The mrTRG score on true HRT2 scans has been shown to correlate with patient outcomes.[6] Although there is a lower correlation between pathTRG and mrTRG, the predictive nature of an imaging biomarker is more useful when identifying patients suitable for watch and wait.[6,19] The newer concept of a clinical "near-complete response" does not match any current MRI category, describing patients who are mrTRG3 but with only minimal tumor.[20] The "split scar sign" shows promising early results for predicting a sustained clinical response[21] and is currently being assessed prospectively in the RENO trial.[22]

A follow-up MRI imaging schedule for patients is still under investigation, but a reasonable approach is 3-monthly for year 1 and 6-monthly for years 2–5.[20] Some continue 3-monthly in year 2, and others reduce to annual for years 4 and 5, but further data is needed to define the optimal protocol to detect regrowth.

3 | MANAGEMENT OF EARLY LOW RECTAL CANCER: IS THERE A ROLE FOR TNT?

3.1 | AGITG MDT surgical debate

3.1.1 | Case

A 39-year-old female presents with rectal bleeding. The digital rectal examination demonstrates a low rectal mass at the top of the sphincter complex.

Colonoscopy and biopsy confirm adenocarcinoma with preserved mismatch repair and wild-type BRAF status. Initial computed tomography (CT) staging shows no evidence of metastatic disease, and magnetic resonance imaging (MRI) stages the tumor as cT2N0 low rectal lesion at 2 cm from the anal verge, with no EMVI or lateral nodes. She has a family history of bowel cancer, with her mother dying in her 60s of this. She has a personal history of pseudo-obstruction postpartum, complicated by perforation of her caecum and requiring a right hemicolectomy. She has expressed a preference to avoid a stoma if possible but would agree to it if necessary.

Discussion: management of early-stage disease

Current guidelines for early rectal cancer recommend that patients with low-lying tumors are managed with surgical resection.[23–25] Five-year OS rates of greater than 90% may be expected after resection alone.[26] Although resection offers good oncological outcomes in low rectal cancer, it is associated with significant toxicity, morbidity, and quality of life implications, including a high chance of requiring a temporary or permanent stoma, as well as moderate rates of long-term urinary and sexual dysfunction, and low anterior resection syndrome (LARS). In the case of very low tumors, some studies do suggest a higher local recurrence rate with surgery alone due to narrower margins[27] and advocate neoadjuvant CRT to address this.[28] To date, no guidelines have recommended preoperative CRT with a view to a nonoperative management approach in early rectal cancer. Conversely, in advanced rectal cancer, treatment intensification in the form of TNT is becoming increasingly accepted as standard practice.

TNT refers to the loading of all the intended adjuvant chemotherapy preoperatively, either before or after radiotherapy. It has been introduced in the context of locally advanced rectal cancer to improve compliance with chemotherapy and thus afford a better control of the distant disease. The principal logic behind this is that chemotherapy in the adjuvant setting has limited to no benefit in rectal cancer, at least in part due to poor postoperative compliance with treatment.[29] However, although two large randomized controlled trials have shown improvement in DFS at 3 years, there is no long-term data or evidence of improvement in the OS.[2,3,30,31] What is consistently observed is an improvement in the pCR and clinical complete response (cCR) rates.[32]

It is also accepted that in selected patients who meet the criteria for cCR and in the context of a structured surveillance program, a nonoperative organ preservation strategy may be reasonably offered to patients and is cost-effective.[4,33–36] Patients with sustained cCR, if managed nonoperatively, benefit by avoiding the morbidity of surgery and having an improved quality of life compared with patients who had neoadjuvant treatment and surgery.[37] There appears to be little difference in long-term survival overall if a nonoperative management strategy is pursued rather than surgery in patients who achieve cCR, as these patients have a good oncological prognosis either way.[38] However, there is a 15%–20% recurrence rate associated with the nonoperative management.[39] Most of these are local regrowth suitable for salvage surgery, though this surgery may be more complicated due to the delay after radiation.[40] In a small number of patients, recurrence can occur at distant sites, which adversely affects the prognosis.[38] Furthermore, approximately 25% of locally advanced tumors are not responsive to CRT.[41] Arguably, these patients suffer the toxicity of chemoradiation, followed by the morbidity of surgery, and get neither the potential benefit of organ preservation nor the oncologic benefit of radiation.

In contrast to locally advanced rectal cancer, the data for nonoperative management in the context of early rectal cancer is sparse, and therefore, rates of response and recurrence are unclear in this context. However, the best clinical predictors of primary treatment response in advanced rectal cancer are lower T and N stages, and one can expect early-stage tumors to have higher rates of cCR than seen in the locally advanced rectal cancer patient subgroup. Conversely, the stakes are arguably higher, with the administration of neoadjuvant treatment followed by surgery in patients that do not respond, resulting in additional toxicity that could have been reduced by upfront surgery without neoadjuvant treatment.

Management of rectal cancer is becoming increasingly complex with the addition of each new treatment paradigm. This also makes patient counseling challenging. Ultimately, the patient must weigh up the impact of a permanent stoma, potential surgical complications, and quality of life detriment, with the potential additive toxicity of CRT and TNT administered with a view to avoiding surgery. This is a highly individual decision but is influenced profoundly by the way it is proposed and discussed by clinicians. This, in turn, is very specific to the unit and context in which we each practice, with some centers further along in the adoption of TNT than others. The future of early, very low rectal adenocarcinoma appears to be heading toward a similar treatment model as anal squamous cell cancer, where nonoperative management is considered a primary outcome. The key will be predicting the responders and fine-tuning the neoadjuvant therapies and modalities to better cover the spectrum of tumor responsiveness. In the meantime, we must employ a patient-centered approach allowing for all reasonable and available treatment strategies, including upfront surgery and nonoperative management facilitated by TNT, to be discussed with patients so they can make an informed decision that best suits their needs.

3.1.2 | Case

A 33-year-old female presents with rectal bleeding and pain. At the time of work up in the emergency department, she is anemic, and her hemoglobin is 50 g/L. She has lost 10 kg of weight over a 6-month period. She is married with five children and has no major medical comorbidities. On examination, she has a large mass with stigmata from recent bleeding, involving the dentate line and protruding out the anus. There is no pelvic lymphadenopathy. A colonoscopy confirms a non-obstructing low-lying rectal cancer, with a biopsy confirming adenocarcinoma. There is no microsatellite instability. A staging scan does not reveal any evidence of metastasis. A pelvic MRI shows a lesion 9 cm in length extending to the dentate line with prolapse through the anal canal. There appears to be internal anal canal involvement. There are suspicious mesenteric nodes, and there is equivocal EMVI.

Discussion: radiation in locoregionally advanced low rectal adenocarcinoma

Locoregionally advanced low rectal cancers represent between 22% and 38% of rectal cancer patients.[2,3,42] They present a unique and challenging entity, and there are several specific considerations. They can present with significant symptoms, have a higher risk of locoregional relapse after resection, and are more likely to require an abdominoperineal resection.[43] Additionally, the treatment carries a greater risk of morbidity, including incontinence, sexual dysfunction, LARS, and infertility.[44] The importance of appropriate radiation in lower rectal cancers is likely to be higher than in rectal cancers located more proximally.

The argument for long-course chemoradiation

Although the the Trans Tasman radiation oncology group (TROG) trial did not demonstrate a statistically significant difference in locoregional recurrence rates between short-course radiotherapy and long-course CRT, in patients with low-lying rectal cancer, there was a nonsignificant trend toward increased locoregional recurrence when short-course radiotherapy was used.[42] The cumulative local recurrence rates at 3 years in the TROG trial were 7.5% versus 4.4% in the short- and long-course arms, respectively. For low rectal cancers, the local recurrence rates in the TROG trial were 12.5% and 3.2% in the short-course and long-course arms, respectively ($p = 0.26$).[43] This approach is also supported by the results of the RAPIDO study, which showed a locoregional recurrence rate of 8.3% at 3 years in the experimental arm. However, at a median follow-up of 5.6 years, the rate of locoregional recurrence was reported as 10% in the experimental arm (compared to 6% in the standard arm) ($p < 0.05$).[45] The increased locoregional recurrence rates at longer follow-up with short-course radiotherapy emphasize the need for extended follow-up in rectal cancer trials and also the risk for increased locoregional recurrence rates with short-course radiotherapy, even when a TNT approach is employed.

In the lower rectum, the mesorectum is thinner, and even resections achieving a negative CRM margin have a high risk of relapse due to potential surgical seeding, altered lymphatic drainage, and challenging surgery. An analysis of the Dutch TME trial found that lower rectal cancers receiving short-course radiotherapy with the node-positive disease had a risk of local relapse as high as 18% even when CRM was negative.[43] In the case example, there are a number of features concerning for locoregional recurrence and the morbidity associated with it. First and foremost, anatomically, the location in the lower rectum, specifically with anal canal invasion, is a risk factor for locoregional recurrence. A threatened CRM is also an established risk factor for locoregional recurrence. Locoregional recurrences may cause considerable morbidity and are often difficult to salvage. Given that the risk of locoregional recurrence is higher than the risk of systemic recurrence, long-course chemotherapy should be considered as the evidence to support its ability to reduce locoregional recurrences over short-course radiation is building.

3.2 | The argument for short-course radiation

When the risk of systemic failure outweighs the risk of local failure, short-course radiotherapy seems an appropriate strategy. A shorter duration of treatment (5 vs. 25–30 days) allows for faster access to more important chemotherapy and surgery. Short-course radiation followed by surgery remains a reasonable treatment in patients with low risk for distant metastasis.[46] The short-course arms of the Stockholm III study had cumulative LR rates of 2.2%–2.8%, which are very respectable. In patients willing to have a surgical resection, with high-risk features for a systemic spread like EMVI (N1c), N2 disease, and high tumor markers, short-course radiation is an excellent treatment option. The rate of distant metastases was 6.8% lower (26.8% vs. 20%) in the experimental group (short-course radiotherapy followed by chemotherapy, then surgery, then adjuvant chemotherapy) than in the standard of care group (long-course CRT followed by surgery, then adjuvant chemotherapy). This is most likely due to the earlier implementation of meaningful systemic treatment, mitigating the risk of early systemic spread. In the case example, several concerning features are present. The possibility of EMVI and N2 disease is concerning for systemic spread. Raised tumor markers, whilst not always related, do raise suspicion for micrometastases. Short-course radiation allows for the earlier implementation of treatment that will treat micrometastases. It has also been shown to be safe and tolerable in several trials.[2,42,46]

How to optimally utilize radiotherapy during TNT has become an increasingly complex issue and one where several recent publications have not provided the clarity for which they were intended. All decisions regarding radiotherapy are based on patient fitness, symptoms, tumor stage, and patient wishes. In the case example, there are additional challenges. The impact of radiation on sexual function and fertility needs to be discussed with the patients. Depending on the patient's wishes, fertility preservation with oocyte harvesting should be considered. There is no definitive data suggesting less or more toxicity with short-course radiotherapy and long-course CRT. Acknowledging the likely psychosocial factors associated with the diagnosis is critical, and referral to psychosocial support should be encouraged. Radiotherapy has a critical role in preventing locoregional recurrence in low-lying rectal cancer patients. The integration of radiation therapy in TNT is an area that needs further research. Although there are some basic principles that may help decision-making, all decisions need to be tailored to individuals' expectations, wishes, and fitness.

4 | MEDICAL ONCOLOGY DEBATE

4.1 | Case

A 75-year-old Caucasian female had a rectal carcinoma identified from a bowel screening program. She would have thin, frequent stools and blood on the toilet paper for over 6 months, with liquid stools up to

10×/day with urgency and occasional incontinence recently. She reported no abdominal pain, anorexia, or weight loss and lived independently with a WHO performance status of 2. Her current comorbidities included polymyalgia rheumatica for the last 4 years, hypertension, gout, and osteoarthritis, for which she took prednisone (2.5 mg daily), enalapril, celecoxib, and omeprazole.

Clinical examination, including digital rectal exam, was unremarkable. Colonoscopy revealed a partially obstructing tumor involving two thirds of the rectal circumference, 8 cm in length, 9 cm from the anal verge on rigid sigmoidoscopy. A biopsy reported a low-grade adenocarcinoma, proficient for mismatch repair proteins.

Imaging with CT showed no metastatic disease. MRI reported a T4a N1 M0 tumor (T4a by the virtue of the tumor involving the peritoneal reflection), clear of the mesorectal fascia and without visible extramural venous invasion.

4.2 | TNT with consolidation versus induction chemotherapy

The initial management of this elderly woman needs to address threatened rectal obstruction, with a defunctioning colostomy or induction chemotherapy being the main options. The choice depends on the main aims of treatment: maximizing DFS and OS or organ preservation.[47] Another aim to consider is avoiding more treatment than is necessary to achieve these outcomes. This patient's preference was to avoid radical surgery, if possible, without compromising long-term outcomes; these aims are not mutually exclusive. Although the clinical trial evidence to inform these choices is incomplete, there is sufficient evidence to support primary chemoradiation (CRT) with or without consolidation chemotherapy as her best option for achieving these aims.

The best chance of organ preservation and avoiding TME, as demonstrated in the OPRA trial, is by using CRT followed by consolidation chemotherapy.[4] OPRA was, in essence, two stand-alone phase II trials, with patients randomized between them to 4 months of oxaliplatin-based chemotherapy, either before or after CRT. Each arm of the trial was powered to detect 85% 3-year DFS in comparison to 75% in historical controls, an endpoint not achieved in either arm (76% in both). After restaging at the end of TNT, 26% and 24% of patients in the induction and consolidation chemotherapy groups, respectively, were recommended to undergo TME. Among the remaining patients, fewer relapses occurred in the consolidation chemotherapy group, and the proportion of patients with rectal preservation at 3 years was 47% (95% CI, 39–56) after induction chemotherapy and 60% (95% CI, 52–68) after consolidation chemotherapy ($p < 0.05$). Greater antitumor efficacy with 6 weeks of oxaliplatin-based consolidation chemotherapy over induction chemotherapy in patients receiving CRT was also shown in the CAO/ARO/AIO-12 trial.[48] Although this trial did not evaluate organ preservation as an outcome, consolidation chemotherapy achieved a higher pCR rate (25%) than induction chemotherapy (17%).

If this patient accepted a recommendation of CRT followed by consolidation chemotherapy, then, due to the threatened obstruction, she would potentially need a pretreatment defunctioning colostomy. If, however, she elected to have induction chemotherapy, then she has a good chance to avoid a defunctioning colostomy, but at the likely expense of a reduced rectal preservation rate. It is also uncertain that she would gain the DFS (but not OS) advantage shown with 3 months of induction mFOLFIRINOX chemotherapy in the UNICANCER-PRODIGE 23 trial.[5] Although the trial included patients up to 75 years of age, it excluded those with a WHO performance status of 2 or worse and did not include nonoperative management as an alternative to TME. It is doubtful that this patient would tolerate mFOLFIRINOX chemotherapy. Instead, she would likely receive less intensive chemotherapy such as mFOLFOX6 or CAPOX. So, we are back to the evidence derived from the OPRA trial, in which induction chemotherapy was inferior to consolidation chemotherapy for rectal preservation and gave no apparent DFS advantage.[4]

There is an argument for CRT alone in patients who achieve a good response to this approach.[48] For such patients, TNT increases the burden of treatment (longer duration and related toxicity) without clear incremental benefit in cancer outcomes.[20] The challenge lies in identifying patients for whom nonoperative management may be achievable. Imaging, endoscopy, and perhaps, circulating tumor DNA may help identify such patients.[20,49] Similarly, patients identified early with poor tumor response to primary treatment may need treatment intensification or an alternative strategy[50,51]; at the very least, they should not have surgery delayed.[52]

5 | CONCLUSION

Rectal cancer management has undergone a paradigm shift in recent years, with several management approaches available. The previous three cases describe the complexities in the multidisciplinary management of rectal cancer. To select the optimal approach, the treating team should ensure they have high-quality MRI images and reports and consider all the potential options with a patient-centered approach. Patients should be informed of their treatment options and the potential benefits and drawbacks of each. They should be involved in the decision-making process, taking into consideration their personal preferences, values, and goals. When available, participation in clinical trials should be encouraged as the management of rectal cancer continues to evolve. In conclusion, evaluating different treatment approaches, including clinical trials by the multidisciplinary team, involving patients in their care, and considering patients' choices are essential for improving outcomes and quality of life in rectal cancer management.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. 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:iv22-iv40.
2. Bahadoer RR, Dijkstra EA, van Etten B, et al. 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(1):29-42.
3. Conroy T, Bosset JF, Etienne PL, et al. 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(5):702-715.
4. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *J Clin Oncol*. 2022;40(23):2546-2556.
5. Fokas E, Allgäuer M, Polat B, et al. 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(34):3212-3222.
6. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ*. 2006;333(7572):779.
7. https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Rectal_MRI_cancer_report
8. Nougaret S, Jhaveri K, Kassam Z, Lall C, Kim DH. Rectal cancer MR staging: pearls and pitfalls at baseline examination. *Abdom Radiol*. 2019;44:3536-3548.
9. Brown G, Richards CJ, Bourne MW, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. *Radiology*. 2003;227(2):371-377.
10. Rutegård MK, Båtsman M, Blomqvist L, et al. Rectal cancer: a methodological approach to matching PET/MRI to histopathology. *Cancer Imaging*. 2020;20(1):80.
11. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99.
12. Lord AC, D'Souza N, Shaw A, et al. MRI-diagnosed tumor deposits and EMVI status have superior prognostic accuracy to current clinical TNM staging in rectal cancer. *Ann Surg*. 2022;276(2):334-344.
13. Schaap DP, Voogt EL, Burger JW, et al. Prognostic implications of MRI-detected EMVI and tumor deposits and their response to neoadjuvant therapy in cT3 and cT4 rectal cancer. *Intl J Radiat Oncol Biol Phys*. 2021;111(3):816-825.
14. Lord A, Brown G, Abulafi M, et al. Histopathological diagnosis of tumour deposits in colorectal cancer: a Delphi consensus study. *Histopathology*. 2021;79(2):168-175.
15. Schaap D, Boogerd L, Konishi T, et al. Rectal cancer lateral lymph nodes: multicentre study of the impact of obturator and internal iliac nodes on oncological outcomes. *Br J Surg*. 2021;108(2):205-213.
16. Kroon HM, Dudi-Venkata NN, Bedrikovetski S, et al. Malignant features in pretreatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases. *Ann Surg Oncol*. 2022;29:1194-1203.
17. Chand M, Evans J, Swift RI, et al. The prognostic significance of postchemoradiotherapy high-resolution MRI and histopathology detected extramural venous invasion in rectal cancer. *Ann Surg*. 2015;261(3):473-479.
18. Heijnen LA, Maas M, Beets-Tan RG, et al. Nodal staging in rectal cancer: why is restaging after chemoradiation more accurate than primary nodal staging? *Int J Colorectal Dis*. 2016;31:1157-1162.
19. Sclafani F, Brown G, Cunningham D, et al. PAN-EX: a pooled analysis of two trials of neoadjuvant chemotherapy followed by chemoradiotherapy in MRI-defined, locally advanced rectal cancer. *Ann Oncol*. 2016;27(8):1557-1565.
20. Fokas E, Appelt A, Glynne-Jones R, et al. International consensus recommendations on key outcome measures for organ preservation after (chemo) radiotherapy in patients with rectal cancer. *Nat Rev Clin Oncol*. 2021;18(12):805-816.
21. Santiago I, Barata M, Figueiredo N, et al. The split scar sign as an indicator of sustained complete response after neoadjuvant therapy in rectal cancer. *Eur Radiol*. 2020;30:224-238.
22. Vatandoust S, Wattchow D, Sposato L, et al. A longitudinal cohort study of watch and wait in complete clinical responders after chemoradiotherapy for localised rectal cancer: study protocol. *BMC Cancer*. 2022;22(1):222.
23. Glimelius B, Tiret E, Cervantes A, Arnold D. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi81-vi88.
24. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16(7):874-901.
25. Capdevila J, Gómez MA, Guillot M, et al. SEOM-GEMCAD-TTD clinical guidelines for localized rectal cancer (2021). *Clin Transl Oncol*. 2022;24(4):646-657.
26. Tachibana M, Dhar DK, Kinugasa S, et al. Prognosis of patients with T2N0 tumors in the alimentary tract: should they be considered as early cancers? *Digestion*. 2002;66(1):19-22.
27. Baek JY, Yu JI, Park HC, et al. Risk factors for locoregional recurrence in patients with pathologic T3N0 rectal cancer with negative resection margin treated by surgery alone. *Radiat Oncol J*. 2019;37(2):110-116.
28. You YN, Hardiman KM, Bafford A, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Rectal Cancer. *Dis Colon Rectum*. 2020;63(9):1191-1222.
29. Petrelli F, Coinu A, Lonati V, Barni S. A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer. *Int J Colorectal Dis*. 2015;30:447-457.
30. Jin J, Tang Y, Hu C, et al. Multicenter, randomized, phase iii trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). *J Clin Oncol*. 2022;40(15):1681-1692.
31. Ciseł B, Pietrzak L, Michalski W, et al. 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(8):1298-1303.
32. Petrelli F, Trevisan F, Cabiddu M, et al. Total neoadjuvant therapy in rectal cancer: a systematic review and meta-analysis of treatment outcomes. *Ann Surg*. 2020;271(3):440-448.
33. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? *Dis Colon Rectum*. 2013;56(10):1109-1117.

34. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2010;11(9):835-844.
35. Shin JK, Huh JW, Lee WY, et al. Clinical prediction model of pathological response following neoadjuvant chemoradiotherapy for rectal cancer. *Sci Rep*. 2022;12(1):7145.
36. Cui CL, Luo WY, Cosman BC, et al. Cost effectiveness of watch and wait versus resection in rectal cancer patients with complete clinical response to neoadjuvant chemoradiation. *Ann Surg Oncol*. 2022;29(3):1894-1907.
37. Bibi S, Edilbe MW, Rao C. The cost-effectiveness of watch and wait for rectal cancer. *Clin Oncol (R Coll Radiol)*. 2022;35(2):132-137.
38. Fernandez LM, Sao Juliao GP, Figueiredo NL, et al. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. *Lancet Oncol*. 2021;22(1):43-50.
39. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 2018;391(10139):2537-2545.
40. 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(4):e185896.
41. Lu JY, Xiao Y, Qiu HZ, et al. Clinical outcome of neoadjuvant chemoradiation therapy with oxaliplatin and capecitabine or 5-fluorouracil for locally advanced rectal cancer. *J Surg Oncol*. 2013;108(4):213-219.
42. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol*. 2012;30(31):3827-3833.
43. Kusters M, Marijnen CA, van de Velde CJ, et al. Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. *Eur J Surg Oncol*. 2010;36(5):470-476.
44. Croese AD, Lonie JM, Trollope AF, Vangaveti VN, Ho Y-H. A meta-analysis of the prevalence of low anterior resection syndrome and systematic review of risk factors. *Int J Surg*. 2018;56:234-241.
45. Dijkstra EA, Nilsson PJ, Hospers GA, et al. Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared to long-course chemoradiotherapy and surgery—a five-year follow-up of the RAPIDO trial. *Ann Surg*. 2023;10:1097.
46. 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(3):336-346.
47. Bedrikovetski S, Fitzsimmons T, Perry J, et al. Personalized total neoadjuvant therapy (pTNT) for advanced rectal cancer with tailored treatment sequencing based on clinical stage at presentation. *ANZ J Surg*. 2023;93(1-2):173-181.
48. 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(12):djx095.
49. Khakoo S, Carter PD, Brown G, et al. MRI tumor regression grade and circulating tumor DNA as complementary tools to assess response and guide therapy adaptation in rectal cancer. *Clin Cancer Res*. 2020;26(1):183-192.
50. Battersby NJ, Dattani M, Rao S, et al. A rectal cancer feasibility study with an embedded phase III trial design assessing magnetic resonance tumour regression grade (mrTRG) as a novel biomarker to stratify management by good and poor response to chemoradiotherapy (TRIGGER): study protocol for a randomised controlled trial. *Trials*. 2017;18(1):394.
51. Schrag D, Weiser M, Saltz L, et al. Challenges and solutions in the design and execution of the PROSPECT Phase II/III neoadjuvant rectal cancer trial (NCCTG N1048/Alliance). *Clinical Trials*. 2019;16(2):165-175.
52. Deidda S, Elmore U, Rosati R, et al. Association of delayed surgery with oncologic long-term outcomes in patients with locally advanced rectal cancer not responding to preoperative chemoradiation. *JAMA Surg*. 2021;156(12):1141-1149.

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