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REVIEW ARTICLE

Total neoadjuvant therapy: A new standard of care for locally advanced rectal cancer?

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ABSTRACT

Delivering chemotherapy before surgery is a newer treatment approach called total neoadjuvant therapy (TNT), and the National Comprehensive Cancer Network guidelines recommend it for locally advanced rectal cancer (LARC) with cT3 / cN+ / cT4, in contrast with the European Society for Medical Oncology guidelines, in which most rectal cancers can be treated with surgery alone if good quality mesorectal resection is assured. Neoadjuvant or adjuvant treatments are reserved for patients with high-risk tumours, including cT3c/d or cT4, or that threaten the mesorectal fascia. The favourable outcomes in the RAPIDO trial for high-risk rectal cancers with a lower incidence of distant metastasis in the TNT group were observed but with an unexpected increase in the local recurrence with more extended follow-up. This suggests early surgery for nonresponding tumours. The TNT approach was also evaluated in the OPRA trial with long-course chemoradiotherapy and induction versus consolidation chemotherapy. Half the patients presented complete clinical responses and were enrolled in the watch-and-wait (WW) approach. Given the high number of trials and guidelines in this subject, the multidisciplinary team's decision-making process in rectal cancer management is complex. Looking at the actual data, it was concluded that TNT is not for all patients with LARC and is an option if organ preservation is a priority, although with a high regrowth rate in a WW strategy and increasing risk of distant metastasis, questioning the deleterious effect of deferral of surgery.

Keywords: locally advanced rectal cancer, total neoadjuvant therapy, organ preservation, watch and wait strategy, local regrowth.

Introduction

Locally advanced rectal cancer (LARC) is defined as stage II or III rectal cancer, and due to the location of the rectum deep in the pelvis, local recurrence can occur more frequently. After implementing the total mesorectal excision (TME) concept, the Dutch Rectal Cancer Trial demonstrated in 2001 that short-course preoperative radiotherapy (SCPRT) followed by immediate surgery resulted in a local recurrence rate of 2.4 % compared to 8.2 % in the surgery-only group[1] and remained the treatment paradigm for almost two decades. Despite improved local control rate, no impact on disease-free survival was observed with SCPRT or long-course chemoradiotherapy (LCCRT). The optimal timing of surgical resection of LARC after SCPRT or LCCRT remains controversial. Longer intervals after SCPRT or LCCRT may enhance pathologic complete regression (pCR) rates, with unknown prognostic implications, but delays the use of postoperative systemic adjuvant chemotherapy with risks of subsequent metastases and increased surgical morbidity.[2,3] While the National Comprehensive Cancer Network[4] recommends adjuvant chemotherapy for patients who undergo chemoradiotherapy (CRT) and surgery regardless of surgical pathology results, its role in improving outcomes is not well established. Although the level of scientific evidence for sufficient benefit is much lower than in colon cancer, it is reasonable to consider adjuvant chemotherapy in rectal cancer patients after preoperative SCPRT/LCCRT with high-risk yp stage II and stage III.[2]

Delivering chemotherapy before surgery is a newer treatment approach called total neoadjuvant therapy (TNT), which aims to improve compliance with systemic chemotherapy and treat micrometastasis earlier.[5,6] Surgery can safely be delayed after SCPRT/LCCRT, creating a window of opportunity to deliver chemotherapy preoperatively instead of postoperatively. TNT was adopted recently by the National Comprehensive Cancer Network guidelines for rectal cancer in patients with cT3 / cN+ / cT4.[4]

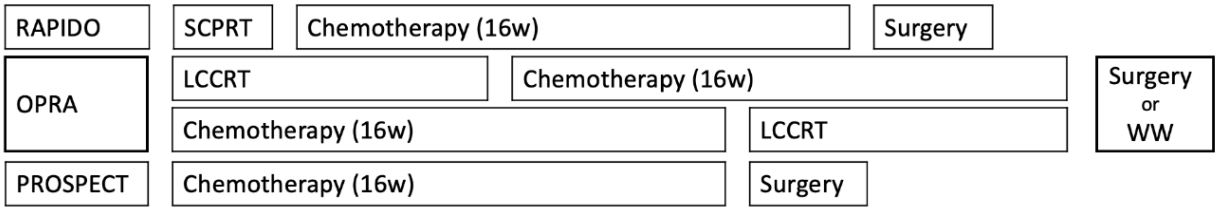
A review of the significant trials on TNT was undertaken, and the aim of this study was to evaluate this new paradigm and the watch-and-wait (WW) surveillance.

Total neoadjuvant therapy (TNT) for LARC

The RAPIDO trial[7] was done in 54 hospitals in seven countries. In this trial, 912 patients with high-risk LARC (cT4, extramural vascular invasion, cN2, involved mesorectal fascia or enlarged lateral lymph nodes) were randomly assigned to TNT with SCPRT followed by 16 weeks of consolidation chemotherapy before surgery in comparison with the standard of care group, with LCCRT. At three years, the disease-related treatment failure was lower in the experimental group than in the standard of care group (23.7% *vs* 30.4%), mainly by a decrease in distant metastases. The observed decreased probability of disease-related treatment failure in the experimental group probably indicates the increased efficacy of preoperative chemotherapy instead of adjuvant chemotherapy. Similar results were found in the PRODIGE 23 trial[6] for patients with cT3 and cT4, with induction chemotherapy and LCCRT with surgery and adjuvant chemotherapy versus the standard of care group. They again saw an advantage in the disease-free survival of 76% vs 69%, respectively.

The unexpected results at the 5-year follow-up in the RAPIDO trial,[8] showing an increased risk of local recurrence in the TNT group against the standard of care group (12% vs 8%), justify further refinements of the short-course TNT approach. The explanation for this finding was that fibrotic mesorectum was more frequently observed with increased anastomotic recurrence in the TNT group. SCPRT may not be the best option for high-risk, bulky rectal tumours. It was also suggested that the non-responding tumours might progress during the long preoperative treatment, and early response imaging was advocated, enabling alterations in the therapeutic approach with early surgery.

Figure 1. Experimental treatments for total neoadjuvant therapy. SCPRT: short-course preoperative radiotherapy, LCCRT: long-course chemoradiotherapy, WW: watch-and-wait, w: weeks.



The TNT approach was also evaluated in the OPRA trial[9] for stage II and III rectal cancer with LCCRT and induction versus consolidation chemotherapy. This trial included 324 patients at 18 US institutions, with tumours located mainly at < 5 cm from the anal verge. Upon restaging after treatment, half of the patients presented complete clinical response (cCR) and were enrolled in the watch-and-wait (WW) program. The 5-year disease-free survival was 71% in the induction chemotherapy and 69% in the consolidation chemotherapy,[10] including selective WW for patients with a cCR, and provides similar results compared with historical control patients treated with neoadjuvant CRT, TME, and adjuvant chemotherapy. In this study, the 5-year disease- free survival was similar (64%) for patients with direct TME after restaging and those with TME after regrowth. The same results were observed in other studies,[11,12] in contrast with others,[13] demonstrating that near-cCR or regrow is associated with a poor prognosis.

To minimise short-term and long-term toxic effects of the chemoradiotherapy, the results of the recent PROSPECT trial[14] show that in patients with intermediate-risk LARC (cT2-T3) who were eligible for sphincter-sparing surgery, preoperative FOLFOX was non-inferior to preoperative LCCRT concerning 5-year disease-free survival (FOLFOX 80.8% and LCCRT 78.6%). In this trial, the patients were restaged after finishing neoadjuvant FOLFOX, and those whose primary tumour had decreased in size by less than 20% (9.1%) received LCCRT. The results of the PROSPECT trial suggest that patients with intermediate-risk LARC will be overtreated with TNT. Furthermore, the 940 enrolled patients were asked to fill patient-reported outcomes (PROs) at baseline, during neoadjuvant treatment, and 12 months after surgery.[15] During neoadjuvant treatment, patients treated with FOLFOX experienced less diarrhoea and better bowel function than those treated with chemoradiotherapy. However, they had a higher burden of other symptoms, including fatigue, anxiety, nausea, and neuropathy. After a year or more following surgery, patients assigned to FOLFOX reported

significantly lower rates of fatigue and neuropathy and better sexual function compared with those assigned to chemoradiotherapy. This data will be helpful for patient information and treatment decisions, as those associated with the proposal of organ preservation to prevent surgical complications or associated functional sequelae must be compared with the adverse sphincter and sexual function[16,17] related to chemoradiotherapy without surgery in the WW programme.

Multidisciplinary team discussion

Now, we can understand the difficult decision for the multidisciplinary team (MDT) in rectal cancer management with such a high number of trials and guidelines in this subject. Does the patient need neoadjuvant treatment, and if so, what treatment? Does the patient have adequate clinical and MRI staging? Is the WW strategy a proper selection for the patient? Does the MDT know the surgical team's local recurrent rate? The quality of the radiologist and the surgeon is crucial to present the best options for the MDT discussion and final decision with the patient.

Total neoadjuvant therapy (TNT) is not for all patients with LARC

We see many advantages to following the European Society for Medical Oncology guidelines.[2] With this policy, most rectal cancers can be treated with surgery alone if good quality mesorectal resection is assured by local recurrence ≤5%. Neoadjuvant or adjuvant treatments are reserved for patients with high-risk tumours, including cT3c/d or cT4, tumours that threaten the mesorectal fascia, lateral node-positive or extramural vascular invasion. In contrast with the National Comprehensive Cancer Network guidelines,[4] this strategy demonstrated promising results in some European units that used neoadjuvant treatment in only 22% of the rectal cancer resections[18] based on optimal MRI staging. The Dutch Snapshot Research Group[19] also showed better oncological outcomes after abandoning routine neoadjuvant radiotherapy nationally.

The 5-year results of the RAPIDO trial[8] with the worst local recurrence rate in the TNT arm is a matter of great debate. Despite improved pCR rate (28% versus 14%), most patients in the TNT group had recurrent lesions (11.7% in the TNT group versus 8.1% in the standard of care) in the presacral area or the anastomosis. If surgery becomes more difficult after 20 weeks following SCPRT, a breached mesorectal fascia would facilitate tumour spillage and contribute to the increased local recurrence rate in the TNT arm. This observation could be explained by fragmentation[20] — a response pattern in which the primary macroscopic tumour is partially destroyed. Small groups of possibly viable tumour cells can persist up to 3 cm in all planes surrounding a central ulcer.[21] Fragmentation is common in tumours of a more advanced stage with a larger diameter. It is generally not visible on macroscopic imaging. Given that 62% of patients in RAPIDO had an involved mesorectal fascia at baseline, viable tumour cells can persist in the mesorectum after the long interval between SCPRT and surgery, either outside or distal to the resection margin.[20] Anastomotic recurrences would be expected if such cells were incorporated into the anastomosis or staple line.

A recent meta-analysis[22] provides evidence that supports TNT with SCPRT or LCCRT in

improving pCR rates, as shown in RAPIDO; however, it does not improve survival outcomes. Also, a study of patients with LARC from the National Cancer Database from 2004 to 2015 compared those treated with TNT or neoadjuvant CRT followed by surgery with or without adjuvant chemotherapy.[23] All patients had clinical stage T3 or T4 or node-positive disease. No significant difference in overall survival, pCR, or negative circumferential resection margin was found between the two groups. Other risk factors, such as the distance of the tumour from the anal verge or toxic effects and compliance with chemotherapy, are difficult to compare in several studies. In conclusion, several results suggest that not all patients receive clinical benefits from TNT over the standard SCPRT or LCCRT and adjuvant chemotherapy approach.

Total neoadjuvant therapy (TNT) is an option if organ preservation is a priority.

Organ preservation was achievable in half of the patients with LARC treated with TNT in the OPRA trial[9] without an apparent detriment in survival. Organ preservation with WW at 5 years was 54% in patients treated with LCCRT then consolidation chemotherapy, compared to 39% in those treated with induction chemotherapy then LCCRT, with a 5-year disease-free survival of 71% and 72%, respectively.[10] Notably, 81 patients with regrow (36%) had similar 5-year disease-free survival (64%) with those who underwent TME after restaging.

Watch-and-Wait (WW) strategy and local regrowth

In 2022, the USA's National Comprehensive Cancer Network guidelines included the non-operative WW as an option for cCR[4] and some European countries[24,25] within rigorous surveillance to detect local regrowth and enrolled in prospective registries or clinical trials. In the UK Oncologic Complete Response (OnCoRe) data[26] at 3-year, the local regrow rate was 38%, suggesting the need for better selection of the patients for the WW approach. Otherwise, there are concerns about the higher rate of distant metastases (36%) for those with regrowth compared to 1% for those that do not regrow.[27] The results of the International Watch & Wait Database Consortium[28] also demonstrated that in 793 patients managed with WW, local regrowth was an independent factor associated with worse distant metastases-free survival in the multivariable model.

A comparative study using prospective international multicentric registries[29] to assess the rate of distant metastases in patients undergoing local excision for near-cCR at restaging versus patients undergoing salvage surgery for regrowth, following WW strategy, showed a significant decrease in the distant metastases-free survival in patients undergoing surgery for regrowth (86% versus 70%, respectively), suggesting the deleterious effect of deferral the surgical resection. This seems to be particularly more pronounced when transmural disease (ypT3-4) is present at the time of salvage. An explanation of these discrepancies can be related to how rectal cancer responds to neoadjuvant treatment: shrinkage or fragmentation.[13] Shrinkage in the direction of the mucosa allows adequate monitoring by imaging or endoscopy. Fragmentation by destroying the primary tumour mass and scattered small groups of tumour cells to form a subselection of tumours with a poor outcome is more challenging. The

limited size of the fragments is below the power of resolution on imaging, and surgical treatment might not be radical, resulting in local recurrences and distant metastases.

In conclusion, although the OPRA trial shows hope for organ preservation, it now contrasts with the high rate of near-cCR and regrowth in a WW strategy, a frequent surrogate biomarker of aggressive biology with an increasing risk of distant metastasis.[28,29] Patients should be carefully advised of this potential disadvantage, questioning the deleterious effect of deferral of surgery. With the growing enthusiasm for administering neoadjuvant therapy to all LARC, there is an urgent need for relevant biomarkers that predict therapy response. For example, using molecular biomarkers or circulating tumour deoxyribonucleic acid (ctDNA)[30] to help predict which patients would benefit from TNT and surgery versus WW surveillance can be helpful.

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