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# Total neoadjuvant therapy for each locally advanced rectal cancer?

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**Summary** The treatment paradigm for locally advanced rectal cancer has changed in recent years. Neoadjuvant radiochemotherapy followed by total mesorectal excision and postoperative chemotherapy has been the standard of care since many years. With this multidisciplinary approach the local recurrence rate is low, but the occurrence of distant metastases and impairments of quality of life due to bowel, bladder, and sexual dysfunction are still unresolved problems. The integration of induction or consolidation chemotherapy into the neoadjuvant setting, a watch-and-wait strategy without surgery for patients with clinical complete response, the integration of immunotherapy into the neoadjuvant setting in microsatellite-instable rectal cancer as well as the selective omission of neoadjuvant radiotherapy now represent different treatment options and enable individualization of therapy for locally advanced rectal cancer. Here, we provide an overview of the latest developments in the treatment of locally advanced rectal cancer and a discussion on which patients need more intensive or less intensive therapy.

**Keywords** TNT · Induction/consolidation neoadjuvant therapy · Radiotherapy in rectal cancer · Watch and wait · Immunotherapy in rectal cancer · Total neoadjuvant therapy

## Introduction

The prognosis of locally advanced rectal cancer (LARC), defined as rectal cancers in which no upfront R0 resection and an increased risk of local relapse is expected, has improved over the past 30 years. In the 1990s, the 5-year survival rate was 30–70% after surgery and the local recurrence rate was 15–40% [1]. Total mesorectal excision (TME) and involvement of radiotherapy in the multimodal therapeutic approach reduced the local recurrence rate to 5–8% [2, 3]. Since 2004, neoadjuvant short-course radiotherapy or radiochemotherapy followed by TME and adjuvant chemotherapy has been the standard of care for LARC [4]. This approach offers advantages including tumor shrinkage, higher rates of sphincter preservation, and lower local recurrence, but without consistent effects on disease-free survival (DFS) and overall survival (OS; [5, 6]). Studies of fluoropyrimidine-based radiochemotherapy achieved pathologic complete remission (pCR) rates of 8–19% [4, 7, 8]. The occurrence of distant metastases in 25–30% of cases is still a serious problem. In addition, the administration of adjuvant chemotherapy is more difficult in LARC. Less than 50% of rectal cancer patients complete adjuvant chemotherapy due to toxicities and/or non-compliance [9, 10], which may affect DFS and OS. Intensification of radiochemotherapy by addition of oxaliplatin [11, 12] or bevacizumab [13] to enhance efficacy led to increased toxicity rates without consistent improvement in outcome. Therefore, the focus of studies in the past few years was to intensify neoadjuvant treatment to enhance the outcome by incorporating induction or consolidation chemotherapy before or after neoadjuvant radiotherapy/radiochemotherapy. Furthermore, studies investigate deintensification of therapy for better quality of life to reduce the risk of bowel, bladder, and sexual dysfunction without disadvantages in survival by a watch-and-wait strategy in clinical complete responders after neoadjuvant therapy, a selective omission of neoadjuvant radiotherapy, or neoadju-

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vant immunotherapy in mismatch repair-deficient rectal cancer (dMMR). Today, different approaches are possible and enable more individualization of therapy.

## Total neoadjuvant therapy

The goals of total neoadjuvant therapy (TNT) are to increase response by integrating systemic therapy before surgery, to reduce the risk of distant metastasis, to improve OS, and to improve quality of life by organ-preserving strategies (sphincter-preserving surgery, watch-and-wait for clinically complete response). Currently, several encouraging prospective studies with different TNT concepts and inclusion criteria have been published, but the heterogeneity of protocols make the comparison and interpretation of data rather complex (Table 1). In the Prodige-23 study [14] and the RAPIDO study [15], a significant improvement in DFS or disease-related treatment failure (DRFT) was demonstrated by induction chemotherapy with 6x FOLFIRINOX followed by radiochemotherapy (Prodige-23 study) or by short-term radiation followed by consolidation therapy with 6x CAPOX or 9x FOLFOX (Rapido study) compared with standard radiochemotherapy. Both trials showed more than a doubling of the pCR rate and a reduction of distant metastases. Data on OS from the Prodige-23 trial were presented at ASCO 2023, showing a significant survival benefit in favor of induction chemotherapy [16]. No improvement in OS was shown in the RAPIDO trial. The German CAO/ARO/AIO-12 trial [17] and the OPRA trial [18] compared induction and consolidation chemotherapy. The CAO/ARO/AIO-12 trial compared 3 cycles of induction chemotherapy with FOLFOX followed by radiochemotherapy (oxaliplatin, 5-FU) versus radiochemotherapy followed by consolidation chemotherapy with FOLFOX [17]. Consolidation chemotherapy was superior in terms of increased pCR rates but there were comparable rates of DFS, local recurrence, and distant metastasis. Toxicities were lower and compliance higher in the consolidation group. The ongoing ACO/ARO/AIO-18.1 trial is investigating whether short-term radiation or radiochemotherapy should be used before consolidation chemotherapy. In the OPRA trial, 8 cycles of FOLFOX or 5 cycles of CAPOX were administered as either induction or consolidation chemotherapy and radiochemotherapy. A watch-and-wait strategy was offered to patients with a clinically complete remission. Both groups were formally compared with a historical control group. The aim of the study was to evaluate the optimal sequence of TNT in terms of DFS and organ preservation. The primary endpoint of the study, improvement in DFS, was not met and was comparable in both arms. However, 3-year TME-free survival was better with consolidation chemotherapy. The STELLAR trial [19] compared short-term radiation followed by 4 cycles of CAPOX, surgery, and 2 cycles of adjuvant CAPOX therapy with radiotherapy followed by TME and 6 cycles of adjuvant CAPOX therapy. There was no difference in DFS but the pCR rates and OS were significantly better in the experimental arm. By contrast, no difference was found in the incidence of distant metastases, R0 resection rates, and local recurrence.

## Immunotherapy in the neoadjuvant setting

Recent developments in the therapy of rectal cancer show that the determination of microsatellite status plays a crucial role already at the stage of the diag-

**Table 1** Overview of study details

| | Treatment arms | Assessment of extent of primary tumor by | Inclusion criteria | Included patients | Primary endpoint |
|---|---|---|---|---|---|
| Prodige 23 | 6x mFOLFIRINOX → CRT → 6x mFOLFOX6<br>versus<br>CRT → TME → 12x mFOLFOX6 or 8x Cap | MRI | < 15 cm anal verge<br>cT3 (at risk of local recurrence)<br>cT4 | 231 vs. 230 | DFS at 3 years |
| Rapido | RT → 6x CAPOX or 9x FOLFOX4 → TME<br>versus<br>CRT → TME → 8x CAPOX or 12x FOLFOX4 (optional) | MRI | < 16 cm anal verge<br>cT4a/b<br>EMVI<br>cN2<br>MRF+<br>Enlarged lateral lymph node | 468 vs. 452 | DRTF |
| OPRA | 8x FOLFOX or 5x CAPEOX → CRT → W&W or TME<br>versus<br>CRT → 8x FOLFOX or 5x CAPEOX → W&W or TME | MRI | cT3/4N0<br>cTxN1-2 | 158 vs. 166 | DFS |
| CAO/ARO/AI | 3xFOLFOX → CRT—(45d) → TME<br>versus<br>CRT (90d) → 3x FOLFOX → TME | MRI | < 12 cm anal verge<br>cT3 < 6 cm from the anal verge<br>cT3 c/d<br>cT4<br>or N+ | 156 vs. 150 | pCR |
| STELLAR | SCRT (21w) → 4x CAPOX → TME → 2x CAPOX<br>versus<br>CRT (14w) → TME → 6x CAPOX | MRI | < 10 cm<br>cT3/4 and/or N+ | 302 vs. 297 | DFS |

*Cap* capecitabine, *CRT* chemoradiotherapy, *d* days, *DFS* disease-free survival, *DRTF* disease-related treatment failure, *EMVI* extramural venous infiltration, *MRF* mesorectal facia, *pCR* pathologic complete response, *TME* total mesorectal excision, *W&W* watch and wait

nosis. At ASCO 2022, immunotherapy with dostarlimab, an anti-PD-1 monoclonal antibody, as single-agent neoadjuvant therapy in patients with dMMR locally advanced rectal cancer, was presented [20]. Patients with dMMR stage II-III rectal cancer receive dostarlimab every 3 weeks for 6 months. Patients with a clinical complete response after completion of dostarlimab therapy have nonoperative follow-up. Patients without clinical complete response after 6 months will receive standard radiochemotherapy followed by TME (in the case of residual disease after radiochemotherapy) or non-operative follow-up (in the case of clinical complete remission after radiochemotherapy). Impressive 100% clinical complete response rates were seen in the first 14 consecutive patients without grade 3–4 adverse events. None of these patients needed radiochemotherapy or TME and no recurrences were detected in the follow-up. Although a longer follow-up and a completion of the study are required, this treatment concept may be able to replace chemotherapy, radiation, and surgery in a subgroup of patients with dMMR rectal cancer, and upfront testing of the microsatellite status is recommended.

## *Selective omission of neoadjuvant radiotherapy in LARC*

Besides intensification of therapy in LARC by TNT especially in high-risk patients, the PROSPECT trial [21] investigated a deintensification in patients with low-to-moderate risk of LARC by selective use of radiotherapy in the neoadjuvant setting. In this trial patients with T2 node-positive, T3 node-negative, or T3 node-positive disease who were candidates for sphincter-sparing surgery were included. In the experimental group 6 cycles of neoadjuvant FOLFOX was administered followed by surgery in cases of >20% tumor shrinkage or followed by radiochemotherapy if the tumor decreased by <20% in size or if FOLFOX was not tolerated, followed by surgery and adjuvant chemotherapy. The control arm received radiochemotherapy followed by surgery and adjuvant chemotherapy. In two thirds of patients, the tumor was located in the middle third of the rectum and about 60% of all patients were node positive. Preoperative FOLFOX was noninferior to preoperative radiochemotherapy with respect to DFS, and local recurrence as well as OS were similar in both groups. Only 9% of patients in the experimental arm received neoadjuvant radiochemotherapy after FOLFOX therapy. Bowel and sexual function were better in patients without radiotherapy. The Chinese FOWARC trial [22] is a further study investigating neoadjuvant FOLFOX with or without radiotherapy in stage II-III rectal cancer patients. In this three-arm trial, neoadjuvant radiochemotherapy (fluorouracil vs. FOLFOX) versus neoadjuvant FOLFOX was compared, and neoadjuvant FOLFOX6 with or without radiation did not significantly improve 3-year DFS versus fluorouracil with radiation in patients with LARC and there was no difference in outcomes. However, it should be taken into account that both trials included patients in whom a primary surgery is an option, for example, T3 node-negative tumors in the upper third or T3 a/b-node negative tumors in the middle third of the rectum. Based on these two studies, additional investigations are needed to clarify the role of radiotherapy in neoadjuvant treatment of LARC.

**Table 2** Therapeutic approach in rectal cancer

| Subgroup | Upper third | Middle third | Distal third |
|---|---|---|---|
| *Low risk* (T1-2, N0, without RF) | Upfront surgery | | |
| *Intermediate risk* (T2N1, T3N0-1, MRF-, without RF) | T3N0: Upfront surgery N+: Discussion of CRT or short-course RT or upfront surgery | CRT or short-course RT | CRT or Discussion of TNT |
| *High risk* (T4, N2, MRF+, EMVI+, LN+) | TNT | | |
| *MSI* | Consider immunotherapy | | |
| *cCR after neoadjuvant therapy* | Consider watch-and-wait | | |

*cCR* clinical complete response, *CRT* chemoradiotherapy, *EMVI* extramural venous invasions, *LN* lateral lymph nodes, *MRF* mesorectal fascia, *RF* risk factors, *RT* radiotherapy

## *Practical approach—who needs more intensive or less intensive therapy in LARC?*

A therapeutic approach based on the risk factors, microsatellite status, and location of the tumor in the rectum is summarized in Table 2. Upfront testing of dMMR in LARC makes it possible to offer immunotherapy to selected patients after intensive discussion of the current small sample size and the ongoing study status and should be weighed against the high response rate, good tolerability, and quality of life by avoiding radiotherapy and surgery. If immunotherapy is applied, close response evaluation as in the study is recommended so as to switch to standard radiochemotherapy in the case of insufficient response.

In patients with high-risk factors such as T4, N2 status, mesorectal fascia involvement, extramural vascular invasion, and enlarged lateral lymph nodes, TNT seems to be the preferred therapy strategy. Consolidation TNT shows some advantages over an induction regimen, but differences in long-term survival are still required in order to clarify this highly debated issue. Furthermore, patients with distal tumors are at the highest risk for the need of an abdominoperineal resection with permanent colostomy and the use of TNT may enhance the opportunity for organ preservation and should be discussed even in patients without high-risk factors. Patients with a clinical complete response, a watch-and-wait strategy under close follow-up can be discussed. Clinical complete response is

defined as no palpable tumor material on digital rectal examination, no residual tumor material or only a small residual erythematous ulcer or scar at rectoscopy, substantial downsizing with no observable residual tumor material, or residual fibrosis only (with limited signal on diffusion-weighted imaging), sometimes associated with residual wall thickening owing to edema and no suspicious lymph nodes on magnetic resonance imaging [24]. Follow-up recommendations include measurement of serum carcinoembryonic antigen every 3 months in the first 3 years and then every 6 months in year 4–5; digital rectal examination + endoscopy + pelvic magnetic resonance imaging every 3–4 months in year 1–2 and then every 6 months in year 3–5; and computer tomography after 6 and 12 months and followed up annualy until year 5 [24]. For rectal cancer lying in the upper third of the rectum, upfront surgery is still an option due to the low incidence of local recurrence. Neoadjuvant and adjuvant therapy are reserved for patients with high-risk tumors. For all other LARC patients without high-risk factors, standard radiochemotherapy or radiotherapy followed by surgery and adjuvant chemotherapy is standard of care. The NCCN guidelines [23] recommend a more intensive approach and TNT is offered for any T3 or T4 disease or with node-positive T1 or T2 disease. The selective omission of neoadjuvant radiotherapy and the administration of neoadjuvant chemotherapy in the upper and middle third of the rectum in low-to-moderate-risk LARC patients as in the PROSPECT trial [21] or FOWARC trial [22] are currently not a standard approach and the role of neoadjuvant radiotherapy in this situation has to be clarified.

## Take-home message

Recent studies investigating total neoadjuvant therapy, watch-and-wait approach, immunotherapy, and selective use of radiotherapy allow for more individualization of therapy in locally advanced rectal cancer. Further studies have to clarify which therapy approach is the best in which situation.

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