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Short-course radiotherapy as part of total neoadjuvant therapy for locally advanced rectal cancer – a new standard?

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Selection of optimal perioperative treatment for rectal cancer remains a subject of controversy. Recently established new rationales for the use of short-course preoperative radiotherapy (SCRT – 25 Gy in 5 fractions), instead of standard long-course preoperative radio-chemotherapy (LCRT-CT), are presented and discussed in the present review. New data suggest that short-course radiotherapy combined with 6 cycles of CAPOX, or 9 of FOLFOX4, at present may be considered the best option for perioperative treatment of high-risk rectal cancer. However, there is a clear need to further optimize preoperative treatment using rapidly evolving markers of treatment response, including microsatellite instability and targetable or predictive tumour mutations.

Key words: rectal cancer, preoperative radiotherapy, total neoadjuvant treatment, chemotherapy, systemic treatment

The rationale for short-course preoperative radiotherapy in rectal cancer

Despite extensive clinical research, that has included several randomized trials, the selection of the optimal perioperative treatment for rectal cancer remains a subject of controversy. While there is quite strong evidence to support the superiority of preoperative radiotherapy compared to postoperative treatment [1–4], several doubts remain over the selection of the optimal preoperative regimen. The origins of this debate are illustrated by the analysis of reduction in incidence of pelvic relapse rates as a function of total radiation dose and overall treatment time, determined based on the outcome of historical studies on preoperative radiotherapy for rectal cancer [5]. The results of the analysis indicate that short-course preoperative radiotherapy (25 Gy in 5.0 Gy per fraction) and long-course preoperative radiotherapy (50.4 Gy in 1.8 Gy per fraction) are, in general, iso-effective in terms of locoregional control, providing the adequate dose increment is delivered in long-course regimens to compensate for the extension in overall treatment time and reduction in the fraction size. The exact contribution of each of these factors (i.e. overall treatment time and fraction size) towards local effectiveness of preoperative therapy is, however, still not well established, although existing studies suggest that subclinical deposits of rectal cancer repopulate rapidly [5] and the fractionation sensitivity of rectal cancer clonogens is relatively high with α/β estimates of approximately 5.0 Gy [6]. Considering the iso-effectiveness of adequately selected short-course and long-course regiments in terms of tumour control, both schedules have keen opponents and supporters. Diverse arguments have been raised (tumour response rate, sphincter preservation rate, early and late tolerance)

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in favour of a preferred option. A third, somewhat less explored option, which will not be further debated in this article, is preoperative treatment of an intermediate duration (e.g. accelerated fractionation or moderate hypofractionation) which, according to some judgements, may be considered as a rationally supported compromise between long and short treatment [6–8].

To further improve the outcome of preoperative treatment, several attempts have been made to combine radiotherapy with chemotherapy, both in concurrent and sequential fashion. The rationale for such a combination is enhancement of the local effectiveness of treatment (usually mild chemotherapy regimens given concurrently to radiotherapy) and a reduction in the rate of distant metastases (mostly intense chemotherapy given sequentially to radiotherapy). One of the earliest prospective studies that explored the effectiveness and tolerance of long-course preoperative radiotherapy combined with chemotherapy (LCRT-CT), as compared to short-course radiotherapy alone (SCRT), was the Polish Colorectal Study Group Trial (Bujko et al. 2004, 2006) [9, 10]. In general, the outcome of this study showed no difference in long-term outcome between SCRT and LCRT-CT. Importantly, despite significant downsizing, chemoradiation did not result in an increased sphincter preservation rate in comparison with SCRT. Considering that the duration of SCRT is shorter compared to LCRT-CT, one could conclude that SCRT is a favourable option, also bearing in mind the labour intensity comparison of both therapeutic protocols.

Similar conclusions could be drawn based on results of the Trans-Tasman Radiation Oncology Group phase III Trial 01.04 (Ngan et al. 2012) [11]. No difference in long-term outcome between SCRT and LCRT-CT was recorded in this trial. Notably, both Polish and Trans-Tasman trial protocols required surgery to be performed shortly after the completion of radiotherapy. This raised some controversies, because delaying surgery after SCRT could potentially increase the response rate and improve the tolerance of treatment. On the other hand, delayed surgery could result in diminished local effectiveness, should repopulation during waiting time for surgery counterbalance the effect of radiotherapy. These concerns were resolved by the Stockholm III trial (Erlandsson 2017) [12], which showed a therapeutic advantage (improved tumour downstaging, and a lower postoperative complication rate) providing surgery was delayed for 4–8 weeks after SCRT, compared to surgery within 1 week after radiotherapy. Based on the outcome of the trials discussed, one could conclude that SCRT with delayed surgery is, at present, the best therapeutic option available for locally advanced rectal cancer, at least considering the evidence-based data from the prospective randomized trials. High incidence of distant metastases after optimal loco-regional therapy necessitates, however, a search for the most effective systemic therapy that can also be safely combined with radiotherapy.

The rationale for preoperative chemotherapy

Several prospective randomized trials evaluated the role of adjuvant postoperative chemotherapy for patients with rectal cancer who underwent preoperative radiotherapy or radio-chemotherapy. In some of these trials, postoperative chemotherapy was given regardless of tumour response to preoperative radiotherapy/radio-chemotherapy, while in the other, chemotherapy was scheduled only for patients with upStage II–III disease. None of the trials demonstrated a statistically significant benefit of chemotherapy for OS or DFS. Two meta-analyses of these trials (Breugom 2015, Bujko 2015) [13, 14] confirmed that postoperative chemotherapy for rectal cancer did not significantly improve overall survival. Unsatisfactory clinical effectiveness of postoperative chemotherapy prompted attempts to deliver chemotherapy before surgery. The biological rationale for neoadjuvant systemic treatment is that subclinical cancer deposits would be eliminated before cytokines released at surgery and wound healing had triggered rapid repopulation of malignant clonogenes.

Early trials of total neoadjuvant therapy (TNT-like treatment)

Based on the aforementioned results of the clinical trials, it was hypothesised that SCRT followed by preoperative chemotherapy and surgery may offer the best outcomes in high-risk rectal cancer. Such hypothesis was tested in a randomized trial performed by the Polish Colorectal Study Group (Bujko 2016, Ciseł 2019) [15, 16]. The trial compared 25 Gy in 5 fractions and three cycles of FOLFOX4, to LCRT-CT (50.5 Gy in 28 fractions) combined with 5-Fu/oxaliplatin-based chemotherapy. Eligibility included cT4 or fixed cT3 cases, only those with middle and low rectal cancer were included. These criteria indicated that only the patients with the highest risk of loco-regional relapses were included; the R0 resection rate was selected as the main trial end point. During the patients' accrual, new data emerged demonstrating no benefit of oxaliplatin addition to preoperative chemoradiation. For this reason, the protocol of the trial was amended to postpone the use of oxaliplatin. Postoperative chemotherapy in both groups was optional, meaning that part of the perioperative treatment was delivered after surgery. For this reason, from the present-day perspective, such therapy cannot be accounted for as total neoadjuvant (TNT) because a substantial part of the systemic treatment was delivered after surgery in some patients. Recent literature refer to such protocols as TNT-like treatment [17]. The long-term outcome of this trial did not demonstrate the superiority of SCRT plus chemotherapy over LCRT-CT, although acute toxicity of the SCRT group was lower than in the control arm.

STELLAR (Jin 2022) [18] is a trial of similar design, SCRT was, however, followed by four courses of CAPOX. Two additional cycles of CAPOX (intravenous oxaliplatin [130 mg/m^2, once a day] on day 1 and capecitabine [1000 mg/m^2, twice a day] from days 1 to 14) were given in the TNT group, while

six cycles of CAPOX were prescribed in the CRT group after surgery. Considering that a significant portion of systemic therapy was delivered after surgery, the proposed schedule should be accounted for as another example of TNT-like therapy. There was no significant difference in metastasis-free survival or locoregional recurrence, but the TNT-like group had better 3-year overall survival than the CRT group. The prevalence of acute grade III–V toxicities during preoperative treatment was 26.5% in the TNT-like group, *versus* 12.6% in the CRT group ($p < 0.001$), meaning that an improvement in OS was achieved at the expense of an approximately twofold increase in toxicity. Another criticism to this treatment schedule is that the origin of survival improvement in the TNT-like arm is unclear, considering that the therapy did not significantly reduce the rate of distant metastases, compared to standard treatment.

Recent trials on total neoadjuvant therapy

As opposed to Polish [15, 16] and STELLAR trials [18], the RAPIDO trial (van der Valk 2020, Bahadoer 2021) [19, 20] took advantage of exploring a more intense neoadjuvant chemotherapy protocol (6 cycles of CAPOX, or 9 of FOLFOX4) that was given after SCRT (25 Gy in 5 fractions) in the experimental arm. Only patients diagnosed with rectal cancer, less than 16 cm from the anal verge, with a high-risk features on MRI were included. While the protocol allowed for 9 cycles of FOLFOX, most of the patients recruited received 6 cycles of CAPOX (capecitabine 1000 mg/m^2 twice daily on day 1–14; and oxaliplatin 130 mg/m^2 *i.v.* on day 1). From the present point of view, intensification of preoperative systemic therapy, as proposed in experimental arm of the RAPIDO trial appears crucial, considering that distant metastases are the most common site cause of treatment failure, and postoperative chemotherapy did not significantly improve the outcome.In the control arm of RAPIDO trial LCRT-CT (50–50.4 Gy in 25–28 fractions) with concomitant capecitabine followed by surgery and optional postoperative chemotherapy (8 cycles CAPOX or 12 cycles FOLFOX4) was used. According to the protocol, the overall treatment duration was 22–24 weeks in TNT, compared to 44–48 weeks in the control arm. The compliance to chemotherapy was considerably better in the experimental arm: 84% of patients in the TNT arm received at least 75% of the prescribed chemotherapy, compared to 58% of those who received postoperative chemotherapy in the control arm [19]. Disease-free survival in STELLAR was significantly improved in the experimental group (23.7% *vs.* 30.4%; HR = 0.75), mostly due to a significant reduction in the rate of distant metastases. There was, however, no significant improvement in overall survival [20].

It is worthwhile mentioning that similar outcomes were presented in non-randomized studies, including matched-pair analysis of SCRT and FOLFOX chemotherapy, compared to LCRT-CT (Markovina 2017) [21]. The meta-analyses of total neoadjuvant therapy (TNT) *versus* standard neoadjuvant chemoradiotherapy for locally advanced rectal cancer (Liu 2021, Kasi 2020, Petrelli 2020) [17, 22, 23], including randomized and non-randomized studies, consistently showed an improved tumour response rate, disease-free survival and tendency for improved overall survival in TNT and TNT-like protocols, as compared to standard treatment.

One of the alternative approaches to TNT with SCRT may be TNT with intense induction preoperative chemotherapy followed by LCRT-CT and surgery. Such a treatment schedule was explored in PRODIGE 23 trial (Conroy 2021) [24]. The patients in the experimental arm received neoadjuvant chemotherapy with FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 2400 mg/m^2 intravenously every 14 days for 6 cycles), chemoradiotherapy (50 Gy during 5 weeks and 800 mg/m^2 concurrent oral capecitabine twice daily 5 days per week), total mesorectal excision, and adjuvant chemotherapy (3 months of modified FOLFOX6 [intravenous oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2, followed by intravenous 400 mg/m^2 fluorouracil bolus and then a continuous infusion at a dose of 2400 mg/m^2 over 46 h every 14 days for six cycles] or capecitabine [1250 mg/m^2 orally twice daily on days 1–14 every 21 days]). This experimental therapy improved the disease-free survival (76% *vs.* 69%; HR = 0.69) and complete response rate, compared to the control arm. A criticisms that might be raised of this protocol is that a substantial part of chemotherapy was given postoperatively. For this reason, the novel therapeutic protocol proposed in the PRODIGE 23 trial can be accounted for as TNT-like, and not "true" TNT treatment. Another criticism refers to the duration of the therapy: it takes at least 31 weeks to complete PRODIGE 23 protocol, compared to 22–24 weeks of therapy offered in the RAPIDO trial. An attempt to compare the studies of TNT with SCRT and LCRT-CT was provided in the Liu meta-analysis [17]. While such effort has several limitations, the only difference found was a higher tumour response rate in SCRT *vs.* LCRT-CT trials. Considering the long duration of PRODIGE treatment and the lack of apparent difference in effectiveness compared to the RAPIDO protocol, bearing in mind that only 32% of the patients in the experimental arm of the PRODIGE 23 trial were aged of ≥65 years, the practical utility of the proposed protocol raises some controversies, at least according to our opinion.

Total neoadjuvant therapy and the potential for organ preservation

One of the outcomes that were significantly improved in the TNT arm of the STELLAR trial, as compared to the control arm, were pathological complete tumour responses (28% *vs.* 14%, OR = 2.37). Notably, an improved rate of CT offers the potential opportunity for organ preservation. This issue is of rising interest, and is further explored in the other trials, specifically dedicated to explore this subject.

An example of such research is a large phase II OPRA trial (Garcia-Aguilar 2020) [25] in which induction preoperative chemotherapy was followed by radio-chemotherapy (INCT-CRT) or radio-chemotherapy was followed by preoperative consolidation chemotherapy (CRT-CNCT). Chemotherapy in both groups consisted of 4 months of infusional fluorouracil-leucovorin-oxaliplatin or capecitabine-oxaliplatin and conventionally fractionated radiotherapy (5000 to 5600 cGy) combined with either continuous infusion fluorouracil or capecitabine during the radiation course. Based on tumour response, the patients were offered either a total mesorectal excision (TME) or active follow-up (watch-and-wait). The three-year DFS MFS and OS were the same in the INCT-CRT and CRT-CNCT groups. The proportion of patients who actually preserved the rectum (TME-free survival) was, however, higher in the consolidation preoperative chemotherapy arm (CRT-CNCT), compared to the induction preoperative chemotherapy (INCT-CRT); the respective proportions were 60% *vs.* 47%, the difference was statistically significant.

The higher organ preservation rate in patients treated with CRT-CNCT compared with INCT-CRT is consistent with results of the other phase II trial (CAO/ARO/AIO-12) which reported a higher rate of pathologic complete response in patients with rectal cancer treated with CRT followed by three cycles of FOLFOX and TME, compared with patients treated with three cycles of FOLFOX followed by CRT and TME [26]. It has been hypothesised that the different time interval from the end of radio-chemotherapy to the assessment of response in INCT-CRT *vs.* CRT-CNCT may be considered a potential factor contributing to the difference in organ preservation between the groups [25].

Future directions

Modern-day clinical oncology has been enjoying, over the last years, rapid expansion of novel therapies and of molecular biomarkers that are of indispensable value in the selection of optimal systemic therapy. Therapy for colorectal cancer is among the beneficiaries of this progress [27]. The selection of treatment schedule in metastatic colorectal cancer is now routinely based on KRAS, NRAS and BRAF mutational status. Anti-EGFR antibodies (cetuximab, panitumumab), VEGF inhibitors (bevacizumab, aflibercept) and the VEGFR tyrosine kinase inhibitor (regorafenib) are among the targeted drugs used in therapy for metastatic disease. The encorafenib and cetuximab combination was recently introduced for therapy of BRAF V600E mutated colorectal cancer based on results of the phase III BEACON trial [28]. Novel therapeutic targets and biomarkers of practical clinical importance include a common KRAS mutation and sotorasib, a small molecule that specifically and irreversibly inhibits KRAS [29]. Other, less common, targetable mutations of therapeutic importance in metastatic colorectal cancer include *NTRK1/2/3*, *ROS1*, *ALK* and *HER2*.

Among the greatest breakthroughs in systemic therapy for colorectal cancer are findings restricted to the relatively small subset (1–6%) of patients who harbour microsatellite instability (MSI): a molecular disorder typical for hereditary syndromes (e.g. Lynch syndrome) related to this disease. MSI is associated with impairment of the functions of the mismatch repair (MMR) genes that are encoding the proteins responsible for DNA repair. Several studies have demonstrated clinical activity of immune checkpoint inhibitors in MSI/MMR-deficient tumours, including colorectal cancer.

Pembrolizumab (PD-1 inhibitor) monotherapy appears to be more effective and better tolerated than chemotherapy in metastatic colorectal cancer patients with MSI, based on the results of phase III Keynote-177 study [30]. Likewise, nivolumab plus low-dose ipilimumab demonstrated very promising clinical activity and good tolerance as a first-line treatment for patients with metastatic colorectal cancer who harbour MSI [31].

While clinical oncology has rapidly implemented most of these innovations in clinical practice, particularly in metastatic patients, radiation oncology for rectal cancer seems to considerably lag behind, at least until recently. The first clinical attempts to combine preoperative radio-chemotherapy with immune checkpoint inhibitors in MSI/MMR-deficient colorectal cancer have, however, already been published, suggesting the promising safety and efficacy of such a combination [32].

One of the most stimulating recent findings, particularly considering the topic of the present article, is the outcome of a prospective phase 2 study in which single-agent dostarlimab, – an anti-PD-1 monoclonal antibody – was administered every 3 weeks for 6 months in patients with mismatch repair-deficient stage II or III rectal adenocarcinoma [33]. Patients who had a complete clinical response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery (watch-and-wait policy). At progression after dostarlimab, chemoradiotherapy was to be used. Surgery would be restricted to those who did not have a complete response to chemoradiotherapy or who locally progressed after achieving a complete response. A total of 12 patients completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients had a clinical complete response, with no evidence of a tumour on the MRI, PET/CT, endoscopy, digital rectal examination, or biopsy. While a longer follow-up is needed to assess the duration of response to dostarlimab, and a prospective phase III trial would be needed to maturely assess the safety and efficacy of the proposed treatment, the outcome of this study confirms that MMR deficient, locally advanced rectal cancer is highly sensitive to single-agent PD-1 blockade. Also, it is increasingly recognized that the above-mentioned studies well designate the future directions and strategies of highly individualized, biomarker-driven, neoadjuvant strategies for locally advanced rectal cancer [34].

Conclusions

Short-course radiotherapy combined with 6 cycles of CAPOX may be considered, at present, as one of the best option for perioperative treatment of high-risk rectal cancer. The use of clinical and molecular predictive markers may help, in the future, to optimize such treatment and help to identify subgroups of patients who may benefit from TNT with SCRT with respect to overall survival, as well as those who may need a different treatment schedule.

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