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REVIEW

Implications of recent neoadjuvant clinical trials on the future practice of radiotherapy in locally advanced rectal cancer

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Abstract

Over the last two decades, the standard treatment for locally advanced rectal cancer (LARC) has been neoadjuvant chemoradiotherapy plus total mesorectal excision followed by adjuvant chemotherapy. Total neoadjuvant treatment (TNT) and immunotherapy are two major issues in the treatment of LARC. In the two latest phase III randomized controlled trials (RAPIDO and PRODIGE23), the TNT approach achieved higher rates of pathologic complete response and distant metastasis-free survival than conventional chemoradiotherapy. Phase I/II clinical trials have reported promising response rates to neoadjuvant (chemo)-radiotherapy combined with immunotherapy. Accordingly, the treatment paradigm for LARC is shifting toward methods that increase the oncologic outcomes and organ preservation rate. However, despite the progress of these combined modality treatment strategies for LARC, the radiotherapy details in clinical trials have not changed significantly. To guide future radiotherapy for LARC with clinical and radiobiological evidence, this study reviewed recent neoadjuvant clinical trials evaluating TNT and immunotherapy from a radiation oncologist's perspective.

Key Words: Rectal cancer; Neoadjuvant therapy; Radiotherapy; Total neoadjuvant treatment; Immunotherapy

Core Tip: In locally advanced rectal cancer (LARC), recent randomized controlled trials have demonstrated the benefits of total neoadjuvant treatment (TNT) in terms of oncologic outcomes and organ preservation. The results of clinical trials of immunotherapy suggest the possibility of pelvic radiotherapy in combination with immunotherapy for LARC. However, the radiotherapy details used in clinical trials have not changed significantly. This study reviewed recent neoadjuvant clinical trials evaluating TNT and immunotherapy from a radiation oncologist's perspective to guide future radiotherapy for LARC.

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INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) plus total mesorectal excision (TME) has been the standard treatment for locally advanced rectal cancer (LARC) for almost two decades. Although this approach has reduced the local recurrence (LR) rate to < 5%-10%, 20%-30% patients with LARC still experience distant metastasis (DM), a major cause of death[1-3]. Although the role of adjuvant chemotherapy (CT) on survival outcomes has been investigated by several working groups [4,5], the impact of adjuvant CT after neoadjuvant CRT plus TME on survival and ideal candidates for adjuvant CT are unclear[6]. Oxaliplatin-based neoadjuvant CRT, when compared to conventional CRT, showed higher toxicity rates without survival benefit in all phase III trials except one [7-10].

Total neoadjuvant treatment (TNT) and immunotherapy are the two trending issues in the preoperative treatment of LARC. Five phase III randomized controlled trials (RCTs) evaluating the TNT approach have been reported[11-15]. All trials showed significantly higher pathologic complete response (pCR) rates in the TNT group than in the traditional neoadjuvant CRT group. Moreover, two RCTs revealed that TNT significantly improved DM-free survival (DMFS), disease-free survival (DFS), or disease-related treatment failure[13,14]. Several prospective phase I/II studies have reported promising response rates to traditional neoadjuvant treatment combined with immune checkpoint inhibitors (ICIs)[16-19] or ICI alone[20] in LARC, known as an immune-cold tumor.

However, despite these advances in multidisciplinary treatment strategies for LARC, the radiotherapy (RT) details in clinical trials have not changed significantly. Therefore, to guide future RT for LARC with clinical and radiobiological evidence, this study reviewed recent neoadjuvant clinical trials evaluating TNT and ICIs from a radiation oncologist's perspective.

SUMMARY OF RECENT NEOADJUVANT CLINICAL TRIALS

TNT

The TNT approach brings the systemic adjuvant CT to the preoperative period, which can be administered before or after RT. The TNT approach has several clinical advantages in terms of tumor response, organ preservation, distant control, and long-term survival through early administration of intensive chemotherapeutic agents with a high compliance. The treatment protocols and important findings of RCTs evaluating TNT are summarized in Table 1 and Supplementary Table 1.

Three trials compared short-course RT (SCRT) followed by consolidation CT and standard CRT (POLISH II[21], RAPIDO[13], and STELLAR[15]). Between the SCRT + CT *vs* standard CRT groups, both RAPIDO and STELLA showed a higher pCR rate with TNT, which was not different in POLISH II. Notably, 3-year disease-related treatment failure and DMFS were significantly better in the TNT arm of RAPIDO, and 3-year overall survival (OS) was significantly better in the TNT arm of STELLAR. These results support the fact that SCRT followed by consolidation CT with a sufficient RT-to-surgery interval is a good option with a high pCR rate and potential to improve DMFS and OS, although there are differences in stage distributions, duration of consolidation CT, and RT-to-surgery intervals among these trials.

Three trials evaluated the role of induction or consolidation CT in TNT regimens (PRODIGE23[14], CAO/ARO/AIO-12[22,23], and OPRA[24]). PRODIGE23 showed that induction FOLFIRINOX (6 cycles) followed by standard CRT (*vs* standard CRT) was associated with better pCR, 3-year DFS, and 3-year DMFS rates. CAO/ARO/AIO-12 and OPRA reported no differences in DFS, LR, and DM between the induction and consolidation CT groups. However, the pCR rate in CAO/ARO/AIO-12 and 3-year TME-free survival in OPRA were significantly higher in the consolidation group than in the induction group.

Although the TNT approach for LARC has already been adopted in several practice guidelines[25-28], a one-size-fits-all approach would not be appropriate in many real-world clinical scenarios. Based on the results of the aforementioned RCTs of TNT, Hui *et al*[29] and Roeder *et al*[30] introduced their institutional neoadjuvant approach for LARC according to the risk of local and/or distant failure and patients' desire for organ preservation.

Table 1 Recent randomized trials evaluating the total neoadjuvant treatment approach in locally advanced rectal cancer

Trials	Identifier	Patients	Primary endpoint	Treatment arms	Results (arm A *vs* B *vs* C)
POLISH II[11,21]	NCT00833131	cT4 or fixed cT3 (primary or locally recurrent)	R0 resection	A: CRT (5-FU+LV #2) → S (→ CT); B: SCRT → FOLFOX4 #3 → S (→ CT)	R0: 71% *vs* 77% (NS); pCR: 12% *vs* 16% (NS)
FOWARC[12]	NCT01211210	cT3-4 or cN+	3 yr DFS	A: CRT (de Gramont #5) → TME → de Gramont #7; B: CRT (mFOLFOX6 #5) → TME → mFOLFOX6 #7; C: mFOLFOX6 #4-6 → TME → mFOLFOX6 #6-8	pCR: 14.0% *vs* 27.5% *vs* 6.5%; 3 yr DFS: 72.9% *vs* 77.2% *vs* 73.5% (NS); 3 yr LF: 8.0% *vs* 7.0% *vs* 8.3% (NS); 3 yr OS: 91.3% *vs* 89.1% *vs* 90.7% (NS)
RAPIDO[13,109]	NCT01558921	cT4 or MRF+ or N2 or lateral LN+ or EMVI+	3 yr DRTF[1]	A: CRT (cape) → TME → CAPOX #9 or FOLFOX4 #12; B: SCRT → CAPOX #6 or FOLFOX4 #9 → TME	3 yr DRTF: 30.4% *vs* 23.7%[2]; 3 yr DM: 26.8% *vs* 20.0%[2]; pCR: 14% *vs* 28%[2]
PRODIGE23[14]	NCT01804790	cT3-4 Nany	3 yr DFS	A: CRT (cape) → TME → mFOLFOX6 #12; B: FOLFIRINOX #6 → CRT (cape) → TME → mFOLFOX6 #6	3 yr DFS: 69% *vs* 76%[2]; pCR: 12% *vs* 28%[2]
STELLAR[15]	NCT02533271	cT3-4 or cN+	3 yr DFS	A: CRT (cape) → TME → CAPOX #6; B: SCRT → CAPOX #4 → TME → CAPOX #6	3 yr DFS: 62.3% *vs* 64.5% (NS); 3 yr OS: 75.1% *vs* 86.5%[2]; pCR: 11.8% *vs* 16.6%[2]
CAO/ARO/AIO-12[22,23]	NCT02363374	cT3-4 or cN+	pCR	A: FOLFOX #3 → CRT (5-FU+oxaliplatin) → TME; B: CRT (5-FU+oxaliplatin) → FOLFOX #3→ TME	pCR: 17% *vs* 25%[2]
OPRA[24,110]	NCT02008656	cT3-4N0 or cTanyN1-2	3 yr DFS	A: mFOLFOX6 #8 or CAPOX #5→ CRT → WW or TME; B: CRT → mFOLFOX6 #8 or CAPOX #5 → WW or TME	3 yr DFS: 76% *vs* 76% (NS); 3 yr TME-free survival: 41% *vs* 53%[2]
Tang *et al*[68] ongoing	NCT04543695	Stage II-III with at least one high-risk factors: MRF+, T4, N2, lateral LN, EMVI+	Downstaging (yp0-II, cCR)	A: CRT → TME → CAPOX #6; B: CRT → CAPOX #6 → TME or WW; C: CAPOX #6 → CRT → TME or WW	(Preliminary) yp0-II: 77.1% *vs* 84.2% *vs* 57.1%; pCR + sustained cCR: 22.9% *vs* 42.1% *vs* 28.6%
CAO/ARO/AIO-18.1[76] ongoing	NCT04246684	MRI-defined intermediate and high-risk factors: cT3 low rectal (< 6 cm from AV), cT3c/d middle rectal (≥ 6-12 cm), cT4 tumors, Tany middle/low third of rectum with N+, CRM ≤ 1 mm, EMVI+	3 yr organ preservation	A: SCRT → CAPOX #6 or mFOLFOX6 #8 → WW or TME; B: CRT (5-FU+oxaliplatin) → CAPOX #4 or mFOLFOX6 #6 → WW or TME	

[1]Disease-related treatment failure was defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumor, or treatmentrelated death.

[2]Denotes statistically significant differences.

5-FU: 5-fluorouracil; AV: Anal verge; cape: Capecitabine; cCR: Clinical complete response; CRM: Circumferential resection margin; CRT: Chemoradiotherapy; CT: Chemotherapy; DFS: Disease-free survival; DM: Distant metastasis; DRTF: Disease-related treatment failure; EMVI: Extramural vascular invasion; LF: Local failure; LN: Lymph node; MRF: Mesorectal fascia; MRI: Magnetic resonance image; NS: Not significant; OS: Overall survival; pCR: Pathologic complete response; S: Surgery; SCRT: Short-course radiotherapy; TME: Total mesorectal excision; WW: Watch-and-wait.

Immunotherapy

Radiation has immunomodulatory effects on the host immune system in addition to the direct tumor cell killing effect[31,32]. In particular, dendritic cells activated by radiation can present tumor antigens in lymph nodes (LNs) and activate CD8+ T cells, which are important for killing primary or distant tumor cells[31,33,34]. However, upregulation of programmed death ligand 1 (PD-L1) expression in tumor cells by interferon-γ produced by CD8+ T cells can lead to radioresistance[35,36]. Thus, the potential of a combination of ICIs and RT has been investigated in various cancers, including LARC[37]. In addition, neoadjuvant treatment changes colorectal cancer to an immunogenic tumor *via* loss of the mismatch repair (MMR) protein, decrease in mRNA expression levels of MMR-related genes, and increase in the tumor mutational burden (TMB)[38-40]. Several early-phase clinical trials have reported higher response rates to neoadjuvant treatment combined with ICIs for LARC, when compared to historical rates with conventional CRT. Their treatment protocols and important findings are summarized in Table 2 and Supplementary Table 1.

Four trials evaluated tumor response to CRT combined with concurrent and/or consolidation ICIs. Five cycles of consolidation nivolumab after CRT in the VOLTAGE-A phase I/II trial achieved pCR rates of 30% in patients with microsatellite-stable (MSS) and 60% in patients with high microsatellite instability (MSI-H)[16]. Two trials reported pCR

Table 2 Recent prospective clinical trials using immune checkpoint inhibitors as a component of neoadjuvant treatment for locally advanced rectal cancer

Trials	Identifier	Patients	Primary endpoint	Treatment	Results
VOLTAGE-A [16]	NCT02948348	cT3-4 Nany (regardless of MMR status)	pCR	CRT (cape) → Nivolumab #5 → TME (→ mFOLFOX6/CAPOX)	pCR: 30% for MSS, 60% for MSI-H
AVANA[17]	NCT03854799	cN+ or cT4 or high-risk cT3 (CRM ≤ 1 mm, ≤ 6 cm from AV, or T3c/d)	pCR	CRT (cape) + Avelumab #6 → TME	pCR: 23%
R-IMMUNE [18]	NCT03127007	Stage II or III	pCR, safety	CRT(5-FU) + Atezolizumab #4 → S	pCR: 24%
NRG-GI002 [19]	NCT02921256	Stage II or III with at least 1 of the following criteria: cT3-4 ≤ 5 cm from AV, any cT4 or tumor within 3 mm of MRF, cN2, not candidates for sphincter-sparing surgery at presentation	Neoadjuvant rectal score	A: mFOLFOX6 #6 → CRT (cape) → TME; B: mFOLFOX6 #6 → CRT (cape) + Pembrolizumab #6 → TME	NAR score: 14.08 *vs* 11.53 (NS); pCR: 29.4% *vs* 31.9% (NS)
AVERECTAL [41,111,112]	NCT03503630	cT2N+ or cT3-4aNany	pCR	SCRT → mFOLFOX6 + Avelumab #6 → TME	pCR: 37.5%
Lin *et al*[42]	NCT04231552	Stage II or III	pCR	SCRT → CAPOX + Camrelizumab #2 →TME	pCR: 48.1% (13/27), 46.2% (12/26) for pMMR, 100% (1/1) for dMMR
TORCH[43, 113] ongoing	NCT04518280	cT3-4 or cN+	cCR or pCR	A: SCRT → CAPOX + toripalimab #6 → TME or WW; B: CAPOX + toripalimab #2 → SCRT → CAPOX + toripalimab #4 → TME or WW	(Preliminary) cCR + pCR: 81.3% (13/16 MSS patients); group A (n = 7): cCR 1, pCR 4, near pCR 1; group B (n = 9): cCR 4, pCR 4
Cercek *et al*[20] ongoing	NCT04165772	cT3-4 or cN+ with dMMR or MSI-H	cCR, pCR, overall response	Dostarlimab #9 → if cCR → WW; if residual+ → CRT → WW (cCR) or TME (residual+)	cCR: 100%
PRIME-RT[45] ongoing	NCT04621370	cT3b+ or EMVI+ or CRM ≤ 2 mm or a low rectal tumor requiring abdomino-perineal excision	cCR or pCR	A: (SCRT → mFOLFOX6 #6) + durvalumab #4 → S or WW; B: (CRT → mFOLFOX6 #4) + durvalumab #4 → S or WW	
EA2201[46] ongoing	NCT04751370	cT3-4 or cN+ with dMMR or MSI-H	pCR	Ipilimumab/Nivolumab #2 → SCRT → Ipilimumab/Nivolumab #2 → TME	
Qiu[47] ongoing	NCT04636008	cT2 or higher with dMMR or MSI-H	Adverse reaction after neoadjuvant treatment and perioperative complications	SCRT + Sintilimab #3 → TME or WW	

5-FU: 5-fluorouracil; AV: Anal verge; cape: Capecitabine; cCR: Clinical complete response; CRM: Circumferential resection margin; CRT: Chemoradiotherapy; dMMR: Deficient mismatch repair; EMVI: Extramural vascular invasion; MMR: Mismatch repair; MRF: Mesorectal fascia; MSI-H: High microsatellite instability; MSS: Microsatellite stable; NAR: Neoadjuvant rectal; NS: Not significant; pCR: Pathologic complete response; pMMR: Proficient mismatch repair; S: Surgery; SCRT: Short-course radiotherapy; TME: Total mesorectal excision; WW: Watch-and-wait.

rates after CRT with concurrent and consolidation ICIs; 23% in the AVANA phase II trial[17] using 6 cycles of avelumab and 24% in the R-IMMUNE phase Ib/II trial[18] using 4 cycles of atezolizumab. The NRG-GI002 phase II RCT compared two groups of induction mFOLFOX6 (6 cycles) followed by CRT with or without concurrent and consolidation pembrolizumab; the pCR rate was not different between the groups (31.9% *vs* 29.4%)[19]. Two phase II trials evaluating SCRT followed by consolidation CT and ICIs reported the highest pCR rates; 37.5% in the AVERECTAL trial[41] using 6 cycles of mFOLFOX6 plus avelumab and 48.1% in the trial by Lin *et al*[42] using 2 cycles of CAPOX plus camrelizumab. Notably, an ongoing TORCH trial reported a preliminary clinical complete response (cCR) or pCR rate of 81.3% in 16 MSS patients who received SCRT-based induction or consolidation CAPOX plus toripalimab[43]. In addition, these studies enrolled patients regardless of the MMR status, two of which reported the pCR rate according to the MMR status[16,42]. Although these promising results should be verified in large-scale RCTs, the results indicate the potential benefits of the combination of pelvic RT and ICIs in the aspect of organ preservation and survival outcomes, especially for patients with MSS LARC.

Despite the proportion of patients with deficient MMR (dMMR) or MSI-H LARC being as low as 5%-10%, neoadjuvant ICIs with or without CRT or SCRT for dMMR/MSI-H LARC are gaining attention owing to their high response rates[44]. Most recently, Cercek *et al*[20] preliminarily reported that all 12 consecutive patients with dMMR LARC achieved cCR after 9 cycles of dostarlimab and were under watch-and-wait (WW) without CRT, surgery, or any recurrence for 6-25 mo.

Several ongoing trials are evaluating the response rate and toxicities of SCRT combined with ICIs in patients with dMMR/MSI-H LARC[45-47] (Table 2 and Supplementary Table 1).

RT in clinical trials

The RT dose, field, and techniques were similar among the TNT and immunotherapy trials described above (Supplementary Table 1). The clinical target volume (CTV) included the primary tumor, regional LNs, and pelvic regions at risk, as proposed by Roels *et al*[48] and the Radiation Therapy Oncology Group[49], as long as its definition could be confirmed in the protocol or published article. A total dose of 50-50.4 Gy at 1.8-2 Gy per fraction and 45 Gy at 1.8 Gy per fraction were administered to the gross tumor volume (GTV) and elective pelvic areas during CRT, respectively. All trials using SCRT administered 25 Gy in 5 fractions to the CTV. Some studies allowed an additional boost dose to the GTV (up to a total dose of 54-56 Gy). Intensity-modulated RT (IMRT) or 3-dimensional conformal RT (3D-RT) were used. Although the treatment outcomes of the aforementioned clinical trials using these traditional target volumes and RT doses are promising, better outcomes can be achieved if RT parameters can be optimized for TNT and immunotherapy. The factors to be considered when using RT as a part of TNT or in combination with ICIs will be discussed in later sections.

CLINICAL IMPLICATIONS

Paradigm shift of neoadjuvant treatment regiments

Neoadjuvant CRT (45-50.4 Gy in 25-28 fractions concurrently with 5-fluorouracil or capecitabine) has been recommended in LARC as it improves the resectability, sphincter preservation, and local control rates. Although SCRT (25 Gy in 5 fractions without CT) with delayed surgery is considered effective as CRT in terms of sphincter preservation, R0 resection, and local control, SCRT has not been widely used because of insufficient downstaging and high toxicity[50-52]. On the other hand, many efforts have been made to omit or selectively use pelvic RT in LARC to avoid RT-related toxicities[53,54]. LARC with a low risk of LR can be successfully treated without preoperative or postoperative pelvic RT [25]. However, these approaches require radical resection, which is associated with surgery-related complications. In addition, the WW strategy became doubtful when Habr-Gama *et al*[55] reported excellent long-term outcomes of nonoperative management for patients with LARC who achieved cCR after CRT (50.4 Gy with concurrent 5-fluorouracil and leucovorin) in 2004.

Currently, the neoadjuvant treatment paradigm is shifting in several ways owing to the excellent results of TNT trials [56]. TNT regimens combined with CRT or SCRT are recommended by the National Comprehensive Cancer Network guidelines[57] and are increasingly employed in clinical practice[56]. SCRT is regaining attention because of the following advantages when combined with TNT and immunotherapy: Short treatment time, high compliance, few side effects, and potential synergistic effects with immunotherapy. The WW strategy is being accepted in patients achieving cCR after neoadjuvant treatment, owing to the accumulation of clinical evidence supporting the safety of WW[58]. Although there was no difference in DFS, LR, and OS between mFOLFOX6 with or without RT in FOWARC[12] (Table 1 and Supplementary Table 1), a higher pCR rate in patients receiving RT supports the use of pelvic RT with a higher chance of organ preservation. Even in early rectal cancer with cT2-3abN0, CRT or SCRT followed by local excision or WW has achieved excellent pCR or organ preservation rates[59,60]. These trends emphasize the importance of RT in future neoadjuvant treatment regimens for rectal cancers.

Organ preservation

There is a growing demand for organ preservation to avoid surgical complications or permanent colostomy, which translates into an improved quality of life after treatment for LARC. Various efforts have been made to increase the cCR rate[61]: Escalating the radiation dose, increasing the interval between RT and surgery, and adding consolidation CT before surgery[58,62,63]. When combined with conventional CRT, these approaches increase the rate of cCR, but not survival outcomes[64-66].

A meta-analysis revealed that the TNT approach showed a better pCR rate and survival outcomes than conventional CRT[67], suggesting that the TNT approach is a good option for organ preservation with survival benefits. Based on the results of CAO/ARO/AIO-12[22,23] and OPRA[24], consolidation CT is preferred when using CRT in the WW strategy. Preliminary results of a Chinese phase II RCT also showed the highest CR rate (pCR + sustained cCR) in the consolidation group (22.9% in the CRT group *vs* 28.6% in the induction group *vs* 42.1% in the consolidation group)[68].

Although data on the WW strategy after SCRT are limited, SCRT followed by consolidation CT appears to be an option for organ preservation based on the following evidence. SCRT followed by at least 4 cycles of consolidation CT was associated with significantly better pCR and DFS rates than conventional CRT in a meta-analysis[69]. Studies using SCRT followed by consolidation CT reported similar cCR, LR, and TME-free survival rates as those reported in studies using CRT[24,70,71]. Based on the results of a meta-analysis, at least 4 cycles of consolidation CT after SCRT should be considered[69]. However, the optimal duration of consolidation CT needs to be determined to avoid undertreatment or overtreatment.

Based on the high response rates reported in the AVERECTAL[41], Lin *et al*[42]'s, and TROCH[43] trials, despite the limited data on the role of immunotherapy combined with (C)RT, SCRT-based TNT plus ICIs seems plausible for the WW strategy in MSS LARC. In patients who cannot tolerate intensive CT, CRT with concurrent or consolidation ICIs may be an option for organ preservation, given that the pCR rate (23%-30%) of these approaches seems to be higher than that of traditional CRT[16-18]. The results of ongoing trials of SCRT combined with ICIs (Table 2 and Supplementary Table 1) are anticipated because hypofractionated RT has better immunostimulatory effects than prolonged RT; this will be discussed

in a later section. Induction CT combined with ICIs is discouraged based on the results of NRG-GI002[19]. Extremely high response rates (up to 100%) to immunotherapy alone, shown in retrospective[72] and prospective[20] studies, support the use of immunotherapy alone for dMMR LARC. However, in dMMR LARC with high tumor burden, immunotherapy alone may be insufficient to eliminate all the tumor cells in the body when considering the association between tumor burden and the response to immunotherapy[73]; therefore, the combination of RT and immunotherapy may be needed for dMMR LARC. To provide individualized treatment, future trials should focus on identifying the optimal combination of RT, CT, and ICIs.

RT-RELATED ISSUES

Although the treatment outcomes of the aforementioned clinical trials using traditional target volumes and radiation doses are promising, the current practice of RT for LARC may not be optimal for the combination with TNT and ICIs. The following sections provide clinical and radiobiological evidence for the RT details that would be suitable for the combination therapies in LARC.

RT dose without immunotherapy

The current guidelines typically recommend the conventional long-course RT of 50-50.4 Gy in 25-28 fractions with concurrent CT as neoadjuvant treatment for LARC, with a total dose of ≥ 54 Gy in patients with unresectable tumors or patients who desire organ preservation[25,27,57]. Appelt *et al*[74] reported a positive dose-response relationship for pathologic tumor regression, and two meta-analyses revealed a high pCR rate of 24%-28% with a total dose of ≥ 54 Gy (mostly 1.8-2.2 Gy per fraction) with or without CT intensification[66,75]. However, because no dose-response relationship or survival benefit has been proven for a total dose > 54 Gy, the impact of such high doses is unclear[66,75]. In addition, surgical complications can occur more frequently with equivalent dose in 2 Gy fractions > 58.9 Gy[66]. Thus, total doses of 54-56 Gy with induction or consolidation CT have been used in studies with the intent of organ preservation in LARC[24,62,76].

Traditionally, a total dose of 25 Gy in 5 fractions has been used for SCRT as the sole neoadjuvant treatment for LARC, with a pCR rate of approximately 10%[77]. SCRT (25 Gy in 5 fractions) followed by consolidation CT achieved a higher pCR rate (17%-28%) than conventional CRT (12%-14%)[13,15]. A single institutional retrospective study reported that SCRT (25-30 Gy in 5 fractions) followed by FOLFOX or CAPOX achieved a cCR rate of 50%, persistent cCR rate of 79% in the WW cohort, and a 2-year TME-free survival rate of 40% (69% in patients with cCR)[71]. Although the same institute reported a high 1-year cCR rate of 70% in 19 patients who were treated with dose-escalated SCRT (30 Gy to the primary tumor and 35 Gy to the extramesorectal LNs in 5 fractions) followed by FOLFOX or CAPOX[78], further studies are warranted to evaluate the benefits and toxicities of radiation dose escalation in SCRT-based TNT due to a paucity of data in this area.

RT dose with immunotherapy

Recent prospective studies combining ICIs with RT (Table 2) used traditional dose-fractionation schedules in LARC: Conventional RT (45-50.4 Gy with 1.8-2 Gy per fraction) or hypofractionated RT (25 Gy with 5 Gy per fraction). Different immunological effects between conventionally fractionated and hypofractionated schedules have been reported, mainly in murine cancer models.

In a murine colon cancer model (CT26), conventional RT (5 × 2 Gy or 18 × 2 Gy) exerted immunosuppressive effects by upregulating PD-L1 expression in tumor cells and inducing immunosuppressive myeloid cells (myeloid-derived suppressor cells and tumor-associated macrophages 2)[36,79]. The negative impact on local tumor control and survival of mice was reversed by the addition of programmed death receptor-1 (PD-1)/PD-L1 inhibitors to fractionated RT. In addition, the combination of ICIs and CRT is supported by an increase in TMB, a known predictor of response to immunotherapy[80], in patients with LARC treated with neoadjuvant CRT[40,81]. Seo *et al*[40] reported that CRT decreased the mRNA expression levels of 23 MMR-related genes in LARC. Furthermore, loss of the MMR protein has been observed after neoadjuvant CRT for LARC[38-40,82]. These results explain the high pCR rates (23%-30%) of conventional CRT (45-50.4 Gy in 25-28 fractions) combined with ICIs in VOLTAGE-A[16], AVANA[17], and R-IMMUNE[18]. With insufficient data, it is unclear whether RT dose escalation in neoadjuvant CRT for LARC is beneficial.

Hypofractionated RT using a large fractional dose appears to be more efficacious when combined with ICIs, compared with conventional RT. Preclinical studies have reported that various schedules using 5-8 Gy per fraction elicited CD8+ T cell-mediated immune responses effectively in irradiated local tumors and non-irradiated distant tumors (the abscopal effect) when combined with various immunotherapeutic agents[34,79,83]. Dendritic cells had a higher homing ability to lymphoid tissues when they received an RT dose ≥ 5 Gy than when they received 10 × 2 Gy[84]. Radiation-induced lymphopenia is a known negative prognostic factor for tumor response or oncologic outcomes in various solid tumors, including rectal cancer[85-87]. Moreover, persistent lymphocyte depletion is associated with poor treatment outcomes after immunotherapy for various solid tumors[88]. Hypofractionated schedules was associated with less lymphocyte depletion or faster recovery after treatment in several tumor sites[89-92]; this supports the use of neoadjuvant SCRT in combination with immunotherapy over protracted conventional CRT. The higher tumor response rates of SCRT followed by consolidation CT plus ICI in prospective studies[41-43] (*vs* in trials of CRT plus ICIs[16-18]) may facilitate the use of SCRT in the neoadjuvant treatment regimen for LARC, although the exact causes of this difference cannot be explained, except by the difference in the use of consolidation CT. Nonetheless, since it is unknown whether a combination of the traditional regimen of 25 Gy in 5 fractions with immunotherapy is optimal, further studies are warranted to determine

the optimal dose-fractionation regimen, especially in terms of dose escalation.

RT field

Traditional RT fields include GTVs and regional lymphatics with subclinical nodal metastases. When RT is combined with immunotherapy, elective nodal irradiation (ENI) is not recommended for the following reasons. First, irradiation to tumor-draining LNs can reduce RT-mediated immune responses. Tumor-draining LNs where cytotoxic CD8+ T cells are activated by dendritic cells, are important for RT-induced immunologic cell death[33,93]. In a murine melanoma model (B16F10), irradiation to tumors (1 × 10 Gy) and tumor-draining LNs (3 × 3 Gy) reduced the response of both irradiated and non-irradiated tumors compared to tumor-only irradiation[93]. In another murine colorectal carcinoma model (MC38), a single 12-Gy ENI reduced intratumoral infiltration of functional antigen-specific CD8+ T cells[94]. Second, severe lymphopenia, which has a negative effect on immunotherapy, can occur because of the large RT field that includes the elective nodal area[95,96].

Although a CTV including the primary tumor and mesorectum below the S2/S3 interspace was safe in patients with T2 low-lying/T3, N0-N1 rectal cancers without lateral LN metastasis in a prospective phase II trial[97], there is no clinical evidence against ENI in the neoadjuvant setting of LARC. Future studies should weigh the immunologic benefit of no ENI and risk of recurrence following undertreated metastatic LNs. Nevertheless, since the tumor response to whole pelvic RT combined with ICIs is promising in early-phase clinical trials (Table 2 and Supplementary Table 1), long-term patterns of failure and survival data are anticipated.

RT planning

For a long time, radiation oncologists have tried to lower radiation doses to normal pelvic organs to reduce acute and chronic gastrointestinal and genitourinary toxicities after pelvic RT. The importance of lymphocyte-sparing RT has recently emerged in the era of immunotherapy[98]. There are several reasons supporting the need of lymphocyte sparing during the neoadjuvant pelvic RT of LARC. Approximately one-quarter of the proliferating bone marrow of the body is in the pelvis[99]. Permanent aplasia in irradiated bone may occur with irradiations > 30 Gy[100]. Fatty changes in the pelvic bone marrow are a common observation after CRT[101]. Pelvic RT for pelvic malignancies can cause prolonged lymphocyte depletion[102,103].

In addition to the dose-fractionation schedule and target volume size, the pelvic bone marrow and lymphocyte count can be influenced by the dose rate and delivery techniques such as 3D-RT and IMRT. Although IMRT can reduce acute gastrointestinal and genitourinary toxicities in LARC[104,105], it is unclear whether IMRT is superior to 3D-RT in terms of sparing of active bone marrow (or lymphocytes)[86,95]. The estimated mean dose to the entire circulating blood pool after 60 Gy in 30 fractions for glioblastoma was similar for 3D-RT and IMRT with a sliding window technique (2.4 Gy and 2.7 Gy)[95]. Patients with LARC treated with preoperative pelvic RT with helical tomotherapy showed significantly higher rates of post-treatment neutrophil-lymphocyte ratios ≥ 4 than those treated with 3D-RT[86]. The impact of delivery techniques such as volumetric-modulated RT (VMAT) is unclear, which can deliver radiation doses faster with less low-dose spillage than other IMRT delivery modes such as step-and-shoot and sliding window techniques[106]. Kuncman *et al*[107] reported an association between the dose of active bone marrow on magnetic resonance imaging and absolute lymphocyte count nadir and platelet nadir. Huang *et al*[108] reported a lower incidence of acute hematologic toxicity with pelvic bone marrow-sparing IMRT (IMRT with sliding window or VMAT) using dosimetric constraints for the pelvic bone marrow of V10 ≤ 85%, V20 ≤ 65%, and V30 ≤ 45% (VX = volume receiving X Gy) than with non-sparing IMRT in patients with LARC treated with CRT. Therefore, it is necessary to determine the optimal dose constraints for the pelvic bone (or bone marrow) and proper dose delivery techniques to enhance the effects of immunotherapy.

CONCLUSION

Recent phase II/III RCTs have confirmed the benefits of the TNT approach combined with conventional CRT or SCRT in terms of oncologic outcomes and organ preservation in LARC. The results of pros-pective phase I/II studies suggest the possibility of conventional CRT or SCRT in combination with immunotherapy for LARC. Preclinical and clinical evidence suggests the RT details which may be suitable for the neoadjuvant pelvic RT as a part of TNT or in combination with immunotherapy. However, further studies are warranted to identify optimal RT strategies with the potential of maximizing the effects of neoadjuvant treatment with TNT and immunotherapy.

FOOTNOTES

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