Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Research Article

Early Outcomes of Total Neoadjuvant Therapy Involving Short-Course Radiotherapy and Checkpoint Inhibitors, Versus Long-Course Chemoradiotherapy in Locally Advanced Rectal Cancer: A Monocentric Retrospective Study

Meilian Dong* and Yonggang Shi
Department of Radiation Oncology, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe Road, Zhengzhou, 450052, China

***Corresponding author:** Meilian Dong, Department of Radiation Oncology, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe Road, Zhengzhou, 450052, China
Email: fccdongml@zzu.edu.cn

Received: April 18, 2025
Accepted: May 05, 2025
Published: May 08, 2025

Abstract

Background: The management of locally advanced rectal cancer (LARC) has undergone considerable transformation with the advent of total neoadjuvant therapy (TNT). An innovative approach combines short-course radiotherapy and checkpoint inhibitors (SCRT-CI), presenting a potential alternative to traditional long-course chemoradiotherapy (LCRT). This study aims to evaluate the early outcomes associated with these two treatment regimens.

Methods: We conducted a retrospective analysis of 214 patients treated at the First Affiliated Hospital of Zhengzhou University between January 2021 and December 2023. This study included patients with pathologically confirmed cT3-T4N0 or cT2-4N+ rectal adenocarcinoma with an ECOG performance score of 0 or 1. The SCRT-CI group received chemotherapy in combination with immune checkpoint inhibitors following neoadjuvant short-course radiotherapy. We compared clinical data from patients who received SCRT-CI versus those who underwent LCRT, focusing on treatment completion, local recurrence rates, complete remission rates, anal preservation rates, and complications.

Results: The study found that the SCRT-CI group exhibited significantly higher rates of CR (52.6% VS 16.2%, P=0.000), and anal preservation (97% VS 57.9%, P=0.000), alongside a lower local recurrence rate (10.6% vs 2.1%, P=0.041). Notably, the incidence of complications such as anastomotic stricture and pelvic infection was higher in the SCRT-CI (14.8% vs. 5.4%, P=0.038). Further analysis revealed that prior chemotherapy was a significant risk factor for postoperative complications (P=0.000).

Conclusions: SCRT-CI shows promising early outcomes in treating LARC, demonstrating higher rates of tumor response and anal preservation. However, the associated increase in complications highlights the importance of carefully considering treatment sequencing and patient management strategies.

Keywords: Locally advanced rectal cancer; Bispecific antibody immunotherapy; Short-course radiotherapy; Total neoadjuvant therapy; Complete response

Introduction

LARC poses significant treatment challenges, traditionally managed with preoperative LCRT followed by total mesorectal excision (TME). This standard approach has effectively reduced local recurrence rates and improved tumor resect ability [1,2]. The existing literature consistently suggests that TNT might achieve better tumor control and complete remission rate (CR rate), particularly for patients with high-risk features, thereby enhancing the likelihood of rectal organ preservation and improving quality of life [3,4]. However, there is an almost constant rate of distant metastases occurring in 24%–28% of the cases and no overall survival (OS) benefit of local treatment has been demonstrated in single trials, with CR rates remaining less than 30% [2,5].

Recently, anti-PD-1/PD-L1 inhibitors have shown promising results for many kinds of malignant tumors. Recent studies indicate that radiotherapy may enhance tumor elimination by activating local and systemic immune responses, particularly in combination with immune checkpoint inhibitors. There exists a synergistic effect between radiotherapy and immunotherapy, where radiation can increase the release of tumor-specific antigens and elevate the expression of major histocompatibility complex (MHC) proteins on cancer cells. This heightened activity potentially facilitates improved recognition and targeting of tumor cells by immune agents. Furthermore, radiation therapy can reshape the tumor microenvironment, reduce immunosuppressive factors, and promote T cell infiltration.

Citation: Meilian Dong, Yonggang Shi. Early Outcomes of Total Neoadjuvant Therapy Involving Short-Course Radiotherapy and Checkpoint Inhibitors, Versus Long-Course Chemoradiotherapy in Locally Advanced Rectal Cancer: A Monocentric Retrospective Study. Ann Hematol Oncol. 2025; 12(2): 1480.

Conversely, immunotherapy can enhance the radiosensitivity of tumors by normalizing tumor vascularity and alleviating hypoxia [6-8]. Thus, the combination of radiotherapy and immunotherapy holds significant potential for improving treatment outcomes in LARC. An emerging narrative suggests that SCRT-CI could further elevate CR rates due to the immune-stimulatory capacity observed in patients treated with SCRT alone [9-11]. The SCRT can effectively reduce tumor volume quickly, while the checkpoint inhibitors aim to enhance the immune system's ability to target and eliminate residual cancer cells [12,13].

In this study, we retrospectively analyze the early outcomes of total neoadjuvant therapy incorporating SCRT-CI compared to conventional LCRT. We aim to assess the efficacy, safety, and overall impact of this innovative treatment strategy on patient outcomes, with a focus on enhancing tumor response and reducing complications in LARC patients.

Materials & Methods

Patients

Clinical information of 214 patients with LARC diagnosed in the first affiliated hospital of Zheng Zhou university from January 2021 to December 2023 was collected. All of these patients had mid to lower rectal adenocarcinoma and underwent neoadjuvant chemoradiotherapy. A total of 141 patients received SCRT-CI and chemotherapy, while 73 patients received LARC. The clinical stage of rectal cancer at the time of initial diagnosis was confirmed according to the 8th edition of the International Union Against Cancer (UICC)/ American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system.

Eligibility criteria included histopathological confirmed primary rectal adenocarcinoma; ultrasound endoscopy or magnetic resonance imaging (MRI) staged II (T3-4N0) or stage III (T1-4N1-2) with no evidence of distant metastasis; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1; No contraindications of radiotherapy and chemotherapy, molecular targeted therapy, immunotherapy and surgical treatment. Exclusion criteria included inadequate medical history information; ECOG PS > 1; Histopathological confirmed neuroendocrine carcinoma, squamous cell carcinoma and gastrointestinal stromal tumor; Complicated with other malignant tumors; patients with stage I and IV; with the lower border of the tumor more than 10 cm from the anal verge; TME surgery directly after diagnosis. This study is a retrospective analysis; therefore, written informed consent was not obtained from the participants. As this research utilized anonymized medical data for analysis, the requirement for informed consent was waived in accordance with ethical guidelines for retrospective studies. And this study was in accordance with the ethical standards of the institution and with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of the first affiliated hospital of Zheng Zhou university of Research Office (TA2025-057).

Treatment

Preoperative neoadjuvant radiotherapy includes LCRT and SCRT-CI. LCRT and SCRT were performed by volume intensity-modulated ARC therapy (VMAT) or intensity-modulated radiation therapy (IMRT). Patients with mid to low LARC received LCRT, which involved a total prescribed irradiation dose of 45–50.4 Gy delivered in 25–28 fractions. This radiation was administered in daily fractions of 1.8–2 Gy, five consecutive days per week over a treatment period of 5–6 weeks. Concurrent chemotherapy based on either 5-Fluorouracil (5-FU) or capecitabine was administered throughout the duration of the radiation therapy. Following chemoradiotherapy, patients underwent TME surgery or were placed under a watch-and-wait approach, depending on clinical considerations.

SCRT was administered with a total prescribed irradiation dose of 25 Gy, delivered in 5 fractions over 5 consecutive days, without concurrent chemotherapy. This treatment was followed by delayed TME surgery, which was performed more than 6 weeks later. SCRT in conjunction with systemic therapy included both chemotherapy and immunotherapy. The neoadjuvant chemotherapy regimens primarily consisted of capecitabine combined with oxaliplatin (CapOX), as well as standard regimens of oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX4), and modified FOLFOX6 (mFOLFOX6). The immunotherapy utilized in this study included either Levatinib or Camrelizumab (an anti-PD-1 monoclonal antibody). In this study, the efficacy of neoadjuvant therapy was evaluated by a combination of preoperative ultrasound endoscopy, chest computed tomography, pelvic MRI, and/or postoperative pathology.

Statistical Analysis

The CR rate was used to evaluate the efficacy of neoadjuvant therapy, including pathological complete response (pCR) and clinical complete response (cCR). pCR was defined as surgical specimens (including lymph nodes) without any residual cancer cells under the microscope (ypT0N0M0). cCR following neoadjuvant therapy was defined as the absence of any detectable tumor following treatment, assessed through clinical examination, imaging studies, and endoscopic evaluations. Tumor regression grade (TRG) following neoadjuvant therapy was typically assessed according to the guidelines established by the European Organisation for Research and Treatment of Cancer (EORTC) or the College of American Pathologists (CAP). Besides, the anal preservation rate and the incidence of treatment-related adverse events were also explored.

All statistical analyses were performed using SPSS version 25.0 software (IBM Corporation, Chicago, IL, USA). Categorical variables are expressed as frequencies or percentages. Categorical variables were tested by the Chi-square test or Fisher's exact test. A two-sided P value < 0.05 was considered a statistically significant difference.

Results

This study conducted a retrospective analysis of 214 patients who underwent neoadjuvant radiotherapy at the First Affiliated Hospital of Zhengzhou University from January 2021 to December 2023. Statistical analysis of their clinical data was performed. The results indicated that a greater proportion of patients in the SCRT-CI group completed the treatment compared with LCRT (92.2% vs. 83.6%, P=0.047). Additionally, no significant differences were observed in gender composition (P=0.662). However, in terms of age distribution, patients aged over 75 were more likely to opt for long-course chemoradiotherapy (9.2% vs. 26%, P=0.001). The tumor characteristics is listed in Table 1.

Regarding follow-up, the average follow-up duration was 66 weeks for the SCRT-CI and 49 weeks for the LCRT group, with no significant difference identified. The incidence of tumor regression grading (TRG 1-2) was significantly higher in the short-course radiotherapy group than in the long-course treatment group (P=0.005). Notably, the CR rate in the SCRT-CI group were significantly higher than those in the LCRT group (58.7% VS 25%, P=0.000), as so as the anal preservation rate (97% VS 57.9%, P=0.000). A total of 31 patients lost to follow-up were excluded. Furthermore, the local recurrence rate was higher in the LCRT group compared to the SCRT-CI group (4.8% vs. 0.8%, P=0.114), although this difference was not statistically significant. Meanwhile, the distant metastasis rate was higher in the LCRT group compared to the SCRT-CI group, but this difference was also not statistically significant (12.9% vs. 9.9%, P=0.352). Treatment outcomes are presented in Table 2. Additionally, our further analysis revealed that an increased CR rate and TRG was associated with a reduction in both local recurrence and distant metastasis rates. Patients who achieved CR experienced significantly lower local recurrence compared to those who did not achieve CR (0% vs. 11.3%, P=0.003); the distant metastasis rate was also significantly lower (1.4% vs. 19.7%, P=0.000). A similar phenomenon was observed with TRG. Patients with TRG (0-1) regression had lower local recurrence rates (0% vs. 14.8%, P=0.001) and distant metastasis rates (3% vs. 24.1%, P=0.000), as shown in Table 3.

However, in the SCRT-CI group, the incidence rates of anastomotic fistula and pelvic infection were significantly higher than those in the LCRT group (9.9% vs. 1.4%, P=0.014). Further analysis indicated that receiving chemotherapy prior to radiation therapy, which delayed the intervention of radiation therapy, was a significant risk factor for postoperative complications (P=0.029). When analyzing patients who underwent radiotherapy intervention first, there was no significant difference in complication rates between the SCRT-CI and LCRT groups (9.5% vs. 2.6%, P=0.162). Treatment plans and associated side effects are shown in Table 4.

During the retrospective analysis, we observed that the treatment regimens for immunotherapy varied among patients receiving SCRT-CI. Further analysis revealed that excessively prolonging the observation and waiting period or increasing the number of chemotherapies combined with immunotherapy regimens did not lead to any further improvement in the rates of TRG, CR, or anal preservation, as showed in the Table 5.

Discussion

This study presents an in-depth analysis of the early outcomes of total neoadjuvant therapy involving SCRT-CI versus LCRT in patients with LARC. The findings indicate that both treatment modalities offer effective approaches, yet they differ significantly in terms of clinical outcomes and associated complications.

The SCRT-CI regimen demonstrated substantial advantages in several key clinical parameters. Notably, the higher CR rate and anal preservation rate in the SCRT-CI group underscore its potential as an effective neoadjuvant strategy. Notably, in our study, the incidence of tumor regression grading (TRG 1-2) is significantly higher in the SCRT-CI group than in the LCRT treatment group (P=0.007). The CR rate in the SCRT-CI group is significantly higher than those in the LCRT group (52.6% VS 16.2%, P=0.000), as so as the anal preservation rate (97% VS 57.9%, P=0.000). The results are consistent with those reported by Z.Y. Lin [14].

OS is the gold standard end point, but it may require a long follow-up time in clinical practices. To overcome this drawback, surrogate end points have been proposed such as the pathological assessments TRG and CR. A better outcome for rectal cancer patients with CR has been suggested. Maas et al. [15] did a pooled analysis of 3105 patients with rectal cancer, and suggested a better outcome and patients with CR had a 5-year crude DFS of 83.3% compared with 65.6% in those patients without CR. A pooled analysis also supported a lower risk for metastatic disease in patients with CR [16]. The enhanced tumor response, as evidenced by the higher incidence of tumor regression grading (TRG 1-2) in the short-course group, further supports the notion that this approach may lead to more favorable oncological outcomes[17]. In our study, the local recurrence rate and distant metastasis rate were higher in the LCRT group compared to the SCRT combined with immunotherapy group, although this difference was not statistically significant. It is interesting to note that, an increased CR rate is associated with a reduction in both local recurrence and distant metastasis rates in our further analysis. Patients who achieved CR or TRG (0-1) experienced significantly lower local recurrence and distant metastasis rate. These findings suggest that SCRT combined with immunotherapy may provide additional locoregional control compared to the LCRT regimen. The statistically significant reduction in local recurrence rates associated with short-course radiotherapy combined with immunotherapy is particularly noteworthy. The RAPIDO trial also reported similar results [18].

Our findings indicate that while SCRT-CI demonstrates significant efficacy advantages, the associated complication rates present a serious challenge. Specifically, the incidence of anastomotic stricture, anastomotic leakage, and pelvic infections was notably higher in the SCRT group compared to the long-course chemoradiotherapy group (14.8% vs. 5.4%, P=0.038). Previous studies have reported that neoadjuvant radiotherapy can elevate the risk of these complications [19]; however, direct comparisons between the complication rates of SCRT and LCRT have not been extensively investigated. In clinical practice, situations may arise where neoadjuvant chemotherapy or combined immunotherapy is initially chosen but then switched to SCRT upon finding that the treatment is unresponsive. Clinicians often choose SCRT in these scenarios to avoid delaying systemic therapies, including chemotherapy, immunotherapy, or other targeted treatments. However, our statistical results indicate that such a treatment choice significantly increases surgical complications, such as anastomotic leakage or the incidence of pelvic infections (P=0.000). Further analysis revealed that administering neoadjuvant chemotherapy prior to radiotherapy significantly increased the risk of postoperative complications when SCRT was utilized. This finding underscores the importance of individualized treatment strategies in clinical decision-making for different patients. Combining SCRT with systemic therapies could potentially enhance long-term outcomes for patients with LARC. However, to fully realize the benefits of neoadjuvant treatments in improving prognosis, it is crucial to identify the best combinations of chemotherapy, immunotherapy, and SCRT. Our results suggest that for patients demonstrating poor response or local progression after neoadjuvant chemotherapy, opting for LCRT may be a more favorable choice.

It is interesting to note that, our analysis revealed that excessively prolonging the observation and waiting period or increasing the number of chemotherapies combined with immunotherapy regimens did not lead to any further improvement in the rates of TRG, CR, or anal preservation. LARCT-US trial also pointed out that two chemotherapy cycles less do not compromise the results maintaining a high CR-rate [20]. Tao Zhang et al. also indicated that patients were treated with SCRT sequential 2-cycle CapOX plus Camrelizumab treatment, and the pCR was as high as 52.9% [21].

Conclusions

Overall, this study contributes to the ongoing discourse regarding the optimal management of LARC. SCRT-CI significantly increases the rates of TRG, CR, sphincter preservation, and treatment completion compared with LCRT. However, it also notably raises the incidence of anal stenosis and pelvic infection. Further analysis revealed that among the patients receiving SCRT, those who underwent radiotherapy first did not experience a significant increase in adverse reactions, whereas patients who received multiple cycles of chemotherapy or immunotherapy before radiotherapy exhibited an increase in complications. Additionally, analysis showed that prolonging the duration of neoadjuvant therapy or increasing the number of chemotherapies combined with immunotherapy regimens did not improve TRG, CR, or sphincter preservation rates. Therefore, we recommend that for patients selected for neoadjuvant SCRT treatment, a combination of radiotherapy and immunotherapy along with chemotherapy should be adopted, with a treatment duration of 2 to 4 cycles deemed appropriate.

Acknowledgements

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Data was provided within the supplementary information file. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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