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REVIEW

Neoadjuvant Therapy for Organ Preservation in Locally Advanced Rectal Cancer: A Review

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Abstract: Preoperative chemoradiotherapy (CRT) and sphincter-preserving total mesorectal excision (TME) effectively control tumor growth in locally advanced rectal cancer (LARC). However, associated complications can impair the quality of life (QoL) of the patients. Neoadjuvant therapies, such as consolidation neoadjuvant therapy and total neoadjuvant therapy (TNT), can improve tumor regression, potentially achieving a complete response and allowing organ preservation. Emerging clinical data suggest that these approaches can promote long-term cancer control in patients with LARC.

Keywords: preoperative chemoradiotherapy, locally advanced rectal cancer, organ-preservation, consolidation neoadjuvant therapy, total neoadjuvant therapy

Introduction

Chemoradiotherapy (CRT) and total mesorectal excision (TME) are the standard treatment approaches for locally advanced rectal cancer (LARC).[1,2] Despite improvements in local tumor control and survival, this combination therapy cannot effectively control distant metastasis.[3,4] Additionally, TME-associated complications, including long-term bowel, bladder, and sexual dysfunction, considerably impair the quality of life (QoL) of the patients.[2,5] Organ-preservation approaches, such as consolidation neoadjuvant therapy and total neoadjuvant therapy (TNT), can improve functional outcomes and long-term QoL of the patients.[6–8]

The key focus of this article is to present clinical evidence on the positive outcomes of neoadjuvant therapy in patients with LARC. Preoperative neoadjuvant therapy for organ preservation can potentially become the primary treatment option for LARC, providing better functional outcomes and long-term QoL.

The Definition of LARC

LARC is defined as adenocarcinoma identified via endoscopy, with distal margin no more than 15 cm from the anal verge. Additionally, its staging should be consistent with cT3/cT4 N0 or cT (any) cN1/2, as confirmed by endorectal ultrasound or magnetic resonance imaging.[9,10]

Consolidation Neoadjuvant Therapy of LARC

Preoperative Radiotherapy

The following two main preoperative radiotherapy strategies are used for LARC: short-course radiotherapy (SCRT) and long-course radiotherapy (LCRT). The irradiation dose for SCRT is 25 Gy in 5 fractions, which is immediately followed by radical TME surgery. LCRT, as a component of conventional CRT, comprises 45–50 Gy at 1.8–2 Gy/fraction, followed by 5-fluorouracil (FU)-based chemotherapy. Radical TME surgery is then performed within 6–8 weeks.[11–14] CRT can improve local rectal cancer control.[13–15] SCRT is considered an alternative therapy to CRT for stage II and III

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rectal cancer but does not contribute to tumor downsizing.[16] In contrast, LCRT, when combined with 5-FU-based chemotherapy, effectively reduces tumor size and promotes sphincter preservation. Hence, LCRT is the preferred option for high-risk patients with cN+ and cT4 stage tumors in the lower region, where sphincter preservation is intended.[12,16] LCRT, along with 5-FU-based chemotherapy, has become a standard neoadjuvant therapy for LARC.

Simultaneous Integrated Boost Intensity-Modulated Radiation Therapy (SIB-IMRT)

Three-dimensional conformal radiation therapy (3D-CRT) is commonly used in clinical practice. Nevertheless, integrated boost methods using modern inverse-planning techniques, such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy, and tomotherapy, have emerged, offering dosimetric advantages compared with 3D-CRT.[17–19] Compared with 3D-CRT, IMRT enhances tumor response by increasing local radiation dose and decreases radiation-induced toxicities by preventing the irradiation of healthy tissues.[20] IMRT increases the pathological complete response (pCR) rate and survival rate.[21,22] Clinical trials on patients with LARC undergoing preoperative CRT with SIB-IMRT have shown favorable prognosis with acceptable toxicity levels.[21–23]

Brachytherapy

Neoadjuvant CRT, along with conventional external beam radiation therapy (EBRT), has become a standard treatment for LARC.[24] Although its efficacy against rectal cancer has improved in the last decade, local tumor control, sphincter preservation, and considerable side effects remain major challenges. The local control rate can be improved by increasing the radiation dose. Endocavitary brachytherapy with EBRT can improve pCR rates in patients with rectal cancer, which can help achieve higher R0 resection rates without severe toxicity.[25–27] Compared with external beam irradiation, endocavitary brachytherapy damps rapidly by delivering a high dose to the tumor and protecting the peripheral tissues from significant damage.[28] This technique can efficiently increase the dose, resulting in higher reactivity and down-staging with manageable acute toxicities in preoperative chemoradiation for LARC. Thus, this can be a preferable option, particularly for elderly patients who cannot undergo intensive chemoradiation.[24,29]

Chemotherapy Intensification

The FU-based regimen is considered the standard neoadjuvant CRT and adjuvant chemotherapy for stage II or III rectal cancer.[30] This regimen includes multiple infusions of 5-FU/leucovorin and oral daily capecitabine.[30,31] Chemotherapy intensification, such as including a second drug, can enhance outcomes and optimize preoperative therapy.[32]

Oxaliplatin is highly effective against colorectal cancer; however, its clinical significance in neoadjuvant CRT remains controversial.[33] Several Phase 3 trials have reported that combining oxaliplatin with 5-FU or capecitabine does not improve local tumor control or provide any survival benefits.[34–37] However, the CAO/ARO/AIO-04 study reported contradictory results.[38] Additionally, oxaliplatin can lead to serious adverse events, such as acute and late peripheral neuropathy.[34]

Irinotecan combined with 5-FU is another regimen used in the preoperative CRT of patients with rectal cancer. However, irinotecan is associated with several toxicities, including diarrhea and neutropenia. In terms of adverse events, irinotecan used in neoadjuvant CRT can exacerbate gastrointestinal toxicities, especially diarrhea. The metabolism of irinotecan is influenced by UDP-glucuronosyltransferase (UGT).[39] The CinClare Phase III trial reported a significant increase in complete tumor response in Chinese patients with the UGT1A1 genotype when irinotecan was given with capecitabine-based neoadjuvant CRT.[40] Moreover, a recent study reported that preoperative CRT with FOLFIRINOX as intensification gained considerable achievements in patients with cT3 or cT4 M0 rectal cancer.[41]

Biologically Targeted Treatment

Presently, neoadjuvant CRT with 5-FU or capecitabine is considered an optimal treatment approach for the management of LARC.[30,42] The clinical efficacies of this standard regimen have garnered increasing attention in the last decade by incorporating biological agents. Because the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) can influence DNA repair, cell proliferation, apoptosis, and angiogenesis, monoclonal antibodies targeting them have been used in neoadjuvant therapy.[43] However, for the treatment of LARC, cetuximab, bevacizumab, and panitumumab are not superior alternatives over standard CRT in neoadjuvant treatment.[43–47]

Immunotherapy

The anti-PD-1 antibody has been approved as a salvage treatment option for solid tumors with metastatic mismatch repair gene deficiency (dMMR) or microsatellite instability (MSI).[48] PD-1 blockade is highly effective against dMMR/MSI-H metastatic colorectal cancer. Additionally, preoperative CRT with immunotherapy can significantly improve pCR in patients with LARC.

Total Neoadjuvant Therapy

TNT can be administered as inductive chemotherapy ahead of CRT or consolidation chemotherapy following CRT. However, TNT should be administered exclusively, delivering all planned radiation therapy and chemotherapy in the preoperative setting. The National Comprehensive Cancer Network recognizes TNT as a substitutive treatment for LARC.[49] TNT has several advantages, such as improved compliance with planned therapy and slower advancement of tumors. It can allow for the early assessment of chemosensitivity and expose occult micrometastases to chemotherapy at an early stage in the disease progression. Due to improved treatment compliance and reduced toxicities, TNT is linked with a significant increase in distant tumor control and survival in patients with LARC.[50] Additionally, TNT can increase the number of candidates for organ preservation.

Summary

Concurrent CRT, along with surgery and adjuvant chemotherapy, can significantly reduce the risk of local recurrence in patients with LARC. Nevertheless, distant metastasis is still considered the major cause of mortality among these patients. Consolidation neoadjuvant therapy and total neoadjuvant therapy are effective preoperative treatments for LARC, particularly for tumors located at lower regions requiring organ preservation. However, neoadjuvant therapy for individual patients warrants further validation.

Data Sharing Statement

Because of no new data created or analyzed in this study, data sharing is not applicable to this article.

Ethics Approval and Consent to Participate

Not applicable, our study is based on open-source public database, and The people's Hospital of Tongnan District Chongqing City does not require research using publicly available data to be submitted for review to their ethics committee, so there are no ethical issues and other conflicts of interest.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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