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Evolution and Controversy of Treatment Mode for Locally Advanced Rectal Cancer: From Traditional Chemoradiotherapy to Total Neoadjuvant Therapy Combined with Immunotherapy Strategy

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Abstract

In recent years, the treatment mode of locally advanced rectal cancer (LARC) has undergone a significant evolution from postoperative adjuvant chemoradiotherapy to neoadjuvant chemoradiotherapy, and then to total neoadjuvant therapy (TNT). Although the traditional mode of "preoperative chemoradiotherapy + surgery + adjuvant chemotherapy" reduces the local recurrence rate, the distant metastasis rate is still high, and the compliance of postoperative adjuvant chemotherapy is poor. By advancing postoperative chemotherapy to preoperative period, TNT has formed "induction chemotherapy + concurrent chemoradiotherapy + surgery" or "concurrent chemoradiotherapy + consolidation chemotherapy + surgery" mode, which has significantly improved the completion rate of treatment and the rate of pathological complete response (pCR). Many studies have shown that induction chemotherapy has the potential to improve disease free survival (DFS) and metastasis control, while consolidation chemotherapy has advantages in organ preservation rate. In addition, breakthroughs have been made in immunotherapy for patients with Mismatch Repair Deficiency (dMMR). Single-agent PD-1 inhibitors can lead to clinical complete response (cCR) in some patients. However, the immunotherapy response of patients with Microsatellite stability (MSS) still needs a breakthrough. The current controversies focus on the selection of chemotherapy timing in TNT mode, the synergistic mechanism of radiotherapy and immunotherapy, and the optimization of precise stratification strategy. In the future, it is necessary to integrate multi-omics data and artificial intelligence models, combined with dynamic efficacy evaluation, to promote individualized treatment decisions, and ultimately achieve the dual goals of survival benefit and function preservation.

Keywords: total neoadjuvant therapy, treatment mode, chemoradiotherapy, immunotherapy

1. Introduction

LARC refers to rectal cancer with full-thickness tumor invasion (T3-4 stage) or regional lymph node metastasis (N+) but without distant metastasis. The standard treatment model of LARC has been changed several times. Before the 1970s, LARC patients were mainly treated with surgery alone. In order to overcome the high local recurrence rate after surgery alone, people began to explore postoperative adjuvant radiotherapy and chemotherapy. In the 1990s, the National Institutes of Health (NIH) issued a consensus, which established "TME surgery + adjuvant chemoradiotherapy" as the standard treatment for LARC. However, the local recurrence rate of LARC patients is still high, and it cannot meet the needs of sphincter preservation. The reason is that the completion rate of postoperative chemotherapy is low, and the downstaging effect of radiotherapy cannot be taken advantage of. Therefore, investigators began to explore the use of postoperative long-course concurrent chemoradiotherapy (LCCRT) before surgery. Subsequently, in the early 20th century, the German

CAO/ARO/AIO-94 study (Sauer R, Becker H, Hohenberger W, et al., 2004) established the important position of preoperative LCCRT (50.4 Gy + 5-FU/ capecitabine) in the treatment of LARC, and then entered the era of neoadjuvant chemoradiotherapy. However, although the current standard treatment (LCCRT + TME surgery + adjuvant chemotherapy) reduces the local recurrence rate of LARC patients, the distant metastasis rate of LARC patients is still high. This is partly due to poor compliance with postoperative adjuvant chemotherapy. Therefore, researchers began to add postoperative adjuvant chemotherapy to preoperative treatment, and since then the treatment of LARC has entered the era of TNT. In addition, the high response rate to immunotherapy has led researchers to look at combining it with chemoradiotherapy. This article systematically reviews the evidence-based progress of treatment modalities, analyzes the current controversy, and provides theoretical basis for the precise treatment of LARC.

2. Evolution of Treatment Modalities

2.1 Era of Postoperative Adjuvant Chemoradiotherapy

Before the 1970s, surgery alone was the main treatment for LARC patients, but the local recurrence rate was high. Therefore, since 1970, people have begun to explore postoperative adjuvant therapy to reduce the local recurrence rate. However, most of the early studies used radiotherapy alone, and the effect was limited. Since 1980, postoperative adjuvant chemoradiotherapy has been gradually developed. The GITSG 7175 trial compared surgery alone, postoperative radiotherapy, postoperative chemotherapy, and postoperative concurrent chemoradiotherapy, and found that postoperative concurrent chemoradiotherapy was significantly superior to surgery alone, chemotherapy alone, or radiotherapy alone in local recurrence control (Thomas P R & Lindblad A S., 1988). In 1990, based on the GITSG 7175 trial, the NIH adopted postoperative concurrent chemoradiotherapy as the standard treatment for LARC, marking the official establishment of the “surgery + adjuvant chemoradiotherapy” model.

2.2 Era of Neoadjuvant Chemoradiotherapy

The advantage of postoperative chemoradiotherapy lies in the clear scope of pathology and tumor bed. However, the poor blood supply of tumor bed, less intestinal peristalsis, and the corresponding high toxic reactions lead to poor compliance with postoperative chemoradiotherapy and high local recurrence rate. Therefore, some scholars began to study preoperative radiotherapy. In the early 21st century, the German CAO/ARO/AIO-94 study compared the “LCCRT+TME surgery” mode with the “TME surgery +LCCRT” mode and found that the preoperative LCCRT combined surgery group had higher overall compliance rate, better local control rate, lower toxicity and higher sphincter preservation rate in patients with low tumors (Sauer R, Becker H, Hohenberger W, et al., 2004). Based on the German CAO/ARO/AIO-94 trial, “LCCRT (50.4 Gy + 5-FU/ capecitabine) +TME surgery + adjuvant chemotherapy” has been listed as the standard treatment mode for LARC, and since then LARC has entered the era of neoadjuvant therapy. The popularity of neoadjuvant therapy marks the shift of the focus of treatment from “postoperative rescue” to “preoperative optimization”, which lays a foundation for subsequent models (such as total neoadjuvant therapy and combined immunotherapy).

2.3 Era of Total Neoadjuvant Therapy

2.3.1 Total Neoadjuvant Therapy and Quasi-Total Neoadjuvant Therapy

Although the local recurrence rate of LARC patients under the standard treatment mode is controlled below 10% (Azria D, Doyen J, Jarlier M, et al., 2017; Bosset J F, Collette L, Calais G, et al., 2006; Martling A L, Holm T, Rutqvist L E, et al., 2000; Dahlberg M, Glimelius B & Pahlman L., 1999), the distant metastasis rate is still as high as about 30% (Azria D, Doyen J, Jarlier M, et al., 2017; Sauer R, Liersch T, Merkel S, et al., 2012; van Gijn W, Marijnen C A, Nagtegaal I D, et al., 2011; Kitz J, Fokas E, Beissbarth T, et al., 2018). Furthermore, moving postoperative chemoradiotherapy to preoperative therapy does not improve the OS of LARC patients. This is in part due to poor adherence to and completion of postoperative adjuvant chemotherapy. Therefore, researchers tried to shift postoperative chemotherapy to preoperative chemotherapy, which derived the concept of induction chemotherapy and consolidation chemotherapy. Since then, the treatment of LARC has entered the era of TNT. TNT refers to bringing all postoperative adjuvant treatment to preoperative treatment, that is, from the traditional “preoperative chemoradiotherapy + surgery + adjuvant chemotherapy” to “induction chemotherapy + preoperative chemoradiotherapy + surgery” or “preoperative chemoradiotherapy + consolidation chemotherapy + surgery” treatment mode. However, some studies only add a part of postoperative chemotherapy to preoperative treatment, forming two mixed modes: one is “chemoradiotherapy/radiotherapy + consolidation chemotherapy + surgery + adjuvant chemotherapy” mode, and the other is “induction chemotherapy + chemoradiotherapy/radiotherapy + surgery + adjuvant chemotherapy” mode. These two modes are called TNT -like (Xiao W W & Chen G., 2019). For example, the SCRT group in the POLISH II study (Jin J, Tang Y, Hu C, et al., 2022; Bujko K, Wyrwicz L, Rutkowski A, et al., 2016) and STELLAR study received the mode of “SCRT+ consolidation chemotherapy + TME surgery + (selective) adjuvant chemotherapy”, while the induction

chemotherapy group in the PROGIGE 23 study (Conroy T, Bosset J F, Etienne P L, et al., 2021) received the mode of “induction chemotherapy + LCCRT + TME surgery + adjuvant chemotherapy”. At present, the concept of TNT-like mode only appears in a review by Xiao et al. (2019), while some existing clinical studies confuse the two concepts of TNT mode and TNT-like mode, and generally refer to TNT mode.

2.3.2 Mode of Induction Chemotherapy

Induction chemotherapy refers to the addition of postoperative adjuvant chemotherapy before neoadjuvant chemoradiotherapy. It eliminates subclinical metastatic lesions through early intervention, thereby improving the pCR rate and finally achieving the therapeutic goal of sphincter preservation. The administration mode of induction chemotherapy under the framework of TNT can provide a basis for dynamic adjustment of subsequent concurrent chemoradiotherapy through the evaluation of drug response in vivo. This staged treatment strategy not only contributes to the development of individualized radiotherapy regimens, but also creates a feasibility space for subsequent radiation dose reduction or selective exemption of radiotherapy by screening chemotherapy-sensitive patients, thereby effectively reducing the risk of radiation-related complications (Ominelli J, Valadao M, Araujo R O C, et al., 2021). Grupo Cancer de Recto 3 (GCR3) study from Spain was one of the early systematic studies to explore the application of preoperative induction chemotherapy in rectal cancer. GCR3 study compared the induction chemotherapy group (induction chemotherapy + LCCRT + TME surgery) with the standard treatment group (LCCRT + TME surgery + adjuvant chemotherapy) and found that the two groups of patients had similar OS, DFS, DM, LRR efficacy, but the induction chemotherapy group had lower acute toxicity and higher compliance (Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al., 2015). Based on GCR3 and Cercek (2014) studies, NCCN guidelines added “induction chemotherapy + LCCRT + TME surgery” as one of the treatment recommendations for LARC in 2015. The subsequent PRODIGE 23 study compared the neoadjuvant chemotherapy group (induction chemotherapy + LCCRT + TME surgery + adjuvant chemotherapy) with the standard treatment group (LCCRT + TME surgery + adjuvant chemotherapy) and found that the neoadjuvant chemotherapy group was significantly better than the standard treatment group in terms of overall DFS(P=0.034), overall MFS(P=0.017), pCR (28% vs. 12%, P < 0.0001), serious adverse events during adjuvant chemotherapy (11% vs. 23%, P=0.0049), neurotoxicity(12% vs. 21%, P= 0.032), and tumor regression score(median: 8.4 vs 15.0, p<0.0001), but there was no significant difference in overall OS and overall LRR (Conroy T, Bosset J F, Etienne P L, et al., 2021). Cercek (2018) et al.’s GCR3 study compared the TNT group (induction chemotherapy + LCCRT + TME surgery) with the standard treatment group (LCCRT + TME surgery + adjuvant chemotherapy) and found that the overall CR rate of the TNT group (36% vs. 21%, P < 0.001) was better than that of the standard treatment group. And this advantage still existed after eliminating the confounding factor of operation time (41% vs. 27%, P=0.004). In addition, Cercek et al. found that patients in the TNT group were significantly better than those in the standard-care group in terms of ostomy closure time (median: 89 days vs. 192 days, P < 0.001) and the proportion of minimally invasive surgery (72.2% vs. 47.3%, P < 0.001). Chotard et al. (2021) compared the induction chemotherapy group (induction chemotherapy + LCCRT + TME surgery) with the standard therapy group (LCCRT + TME surgery + adjuvant chemotherapy) and found that the induction chemotherapy mode significantly increased the proportion of pN0 patients (75% vs. 625, P=0.03). In conclusion, induction chemotherapy may improve pCR, MFS and DFS of LARC patients compared with standard treatment.

2.3.3 Consolidation Chemotherapy Mode

Consolidation chemotherapy refers to the advance of postoperative adjuvant chemotherapy to neoadjuvant chemoradiotherapy and surgery, which improves the efficacy through the late reaction of radiotherapy and the addition of systemic chemotherapy. The clinical goal of consolidation chemotherapy is to achieve significant tumor volume reduction, pathological stage improvement, and occult micrometastasis clearance in the neoadjuvant stage. Based on the consolidation chemotherapy regimen of TNT strategy, after the completion of concurrent chemoradiotherapy, the tumor response can be dynamically monitored by imaging and molecular markers, and then the individualized continuous treatment plan can be formulated. Our data show that the prolongation of consolidation chemotherapy cycles is positively correlated with the pCR rate, while there is no statistically significant difference in the incidence of perioperative complications and adverse event spectrum, suggesting that the consolidation chemotherapy mode may provide a new direction (Kim SY, Joo J, Kim T W, et al., 2018; Wang Y, Lou Z, Ji L Q, et al., 2023) for improving the long-term prognosis of patients. The RAPIDO study (Bahadoer R R, Dijkstra E A, van Etten B, et al., 2021) compared the experimental group (SCRT + consolidation chemotherapy +TME) with the standard treatment group and found that the 3-year disease-related treatment failure rate (23.7% vs. 30.4%, P=0.019) and 3-year distant metastasis rate (20.0% vs. 26.8%, P=0.0048) in the experimental group were significantly better than those in the standard treatment group. The POLISH II study (Bujko K, Wyrwicz L, Rutkowski A, et al., 2016) compared the preoperative SCRT plus consolidation chemotherapy group with the standard therapy group and found that the preoperative SCRT plus consolidation chemotherapy group had a better 3-year OS rate than the standard therapy group (73.0% vs.

65.0%, P=0.046). Based on RAPIDO study and POLISH II study, NCCN guidelines recommend SCRT combined with consolidation chemotherapy (CAPOX or FOLFOX) as the recommended regimen for patients with LARC. The subsequent STELLAR study (Jin J, Tang Y, Hu C, et al., 2022) compared the TNT group (SCRT + consolidation chemotherapy + TME surgery) with the CRT group (LCCRT + TME surgery + adjuvant chemotherapy) and found that the TNT group had a better 3-year OS rate (86.5% vs. 75.1%, P=0.033) and overall pCR rate (21.8% vs. 12.3%, P=0.033). TNT was superior to CRT in terms of OS (86.5% vs. 75.1%, P=0.033) and overall PCR rate (21.8% vs. 12.3%, P=0.002). TNT was noninferior to CRT in terms of overall DFS (P < 0.001), while there was no significant difference in 3-year MFS and LRR. In conclusion, consolidation therapy may have a certain value in improving the OS, pCR and DM rates of LARC patients compared with standard therapy.

2.3.4 Comparison Between Induction Chemotherapy and Consolidation Chemotherapy

In terms of some prognostic indicators, induction chemotherapy and consolidation chemotherapy show the possibility of being better than the standard treatment, but whether there is a difference in efficacy between induction chemotherapy and consolidation chemotherapy is still controversial. The CAO/ARO/AIO-12 trial is the first prospective study (Fokas E, Schlenska-Lange A, Polat B, et al., 2022) to report the head-to-head comparison between induction and consolidation chemotherapy. It compared the induction chemotherapy group (chemotherapy +LCCRT+TME surgery) with the consolidation chemotherapy group (LCCRT + consolidation chemotherapy + TME surgery) and found that the consolidation chemotherapy group had a significantly better pCR rate (25% vs. 15%, $P < 0.001$) than historical data. However, direct comparison between the consolidation chemotherapy group and the induction chemotherapy group did not show statistically significant difference (25% vs 17%, P=0.071). These results suggest that consolidation chemotherapy is a better choice for improving pCR rate, but further phase III trials are needed to verify the long-term survival benefit. However, the 3-year follow-up of the CAO/ARO/AIO-12 study (Fokas E, Schlenska-Lange A, Polat B, et al., 2022) showed that the higher pCR rate in the consolidation chemotherapy group did not bring long-term survival benefit. The next CAO/ARO/AIO-18 study will further compare the efficacy of preoperative SCRT combined with consolidation chemotherapy and preoperative LCCRT combined with consolidation chemotherapy. In addition, the OPRA study (Garcia-Aguilar J, Patil S, Gollub M J, et al., 2022) compared LARC patients who received induction chemotherapy (chemotherapy + LCCRT + selective TME surgery) with those who received consolidation chemotherapy (LCCRT + chemotherapy + selective TME surgery) and found that patients who received consolidation chemotherapy achieved a higher 3-year organ preservation rate (41% vs. 53%, P=0.01). However, there were no significant differences in 3-year DFS, OS, DM and LRR between the two groups. The preliminary results of OPRA study suggest that consolidation chemotherapy is more advantageous in tumor regression and organ preservation. The long-term follow-up results of OPRA study showed that the 5-year surgery-free survival rate of the consolidation chemotherapy group was significantly higher than that of the control group (54% vs 39%, P=0.012), but there was no significant difference in 5-year OS, DFS, LRR, and DM between the two groups. This further confirmed that the consolidation chemotherapy mode had the advantage of organ preservation in terms of organ preservation rate, and the survival outcome was not affected by the treatment sequence. In conclusion, for patients with a strong desire for organ preservation, TNT is recommended as the preferred consolidation chemotherapy.

3. Exploration of Neoadjuvant Immunotherapy

3.1 Current Evidence

Approximately 5% to 10% of rectal adenocarcinomas have dMMR, and these patients have a poor response to standard chemotherapy regimens (CercekA, Dos Santos Fernandes G, Roxburgh C S, et al., 2020; Alex A K, Siqueira S, Coudry R, et al., 2017; Alatise O I, Knapp G C, Sharma A, et al., 2021). The use of immune checkpoint blockade alone as a first-line treatment for patients with metastatic colorectal cancer and refractory disease with dMMR has been shown to improve objective response rates and prolong overall survival in such patients (Andre T, Shiu K K, Kim T W, et al., 2020; Le D T, Uram J N, Wang H, et al., 2015; Overman M J, Lonardi S, Wong K Y M, et al., 2018). Based on this finding of benefit in metastatic colorectal cancer, Cercek et al. (2022) explored the use of anti-PD-1 monoclonal antibody alone followed by standard chemoradiotherapy followed by surgery in patients with LARC and dMMR, depending on whether the patient achieved cCR. All 12 patients achieved cCR and were recurrence-free with at least 6 months of subsequent follow-up. The study by Cercek et al. is a pioneer study to explore PD-1 inhibitors as neoadjuvant therapy in LARC with dMMR at an early stage, which lays the foundation for subsequent immunotherapy application. The VOLTAGE-A study (Bando H, Tsukada Y, Inamori K, et al., 2022) is the first clinical study to integrate an immune checkpoint inhibitor (Nivolumab) into the TNT framework in patients with LARC. The treatment model of “LCCRT+ immunotherapy +TME surgery ± adjuvant chemotherapy” has significantly improved the pCR rate of patients with MSS and Microsatellite instability- high (MSI-H), and clarified the predictive value of PD-L1 and

CD8/CTreg ratio. These results provide an important evidence-based basis for the application of immunotherapy in LARC patients, and mark substantial progress in precision immunotherapy in this field.

3.2 Challenges

There are still many challenges in the immunotherapy of LARC. First, the molecular heterogeneity of LARC patients significantly affects the efficacy and universality of immunotherapy. Based on MSI status, LARC patients can be divided into two major subtypes, dMMR/MSI-H and MSS. Although dMMR/MSI-H patients are sensitive to immunotherapy, they account for only 5% to 10% of patients with rectal adenocarcinoma, and some patients are still at risk of drug resistance. However, MSS subtype accounts for more than 90% of patients with rectal adenocarcinoma and has a low response rate to immunotherapy. In addition, the dynamic changes of immune microenvironment (such as up-regulation of PD-L1 expression after radiotherapy) and genomic instability (such as POLE/POLD1 mutation) further increase the complexity of efficacy prediction. Second, the timing of radiotherapy and immunotherapy remains to be resolved. Whether preoperative radiotherapy followed by immunotherapy, preoperative immunotherapy followed by radiotherapy, or radiotherapy combined with immunotherapy is more beneficial to patients and how long the interval between radiotherapy and immunotherapy remains controversial.

4. Conclusions and Prospects

With the continuous evolution of treatment modalities for LARC, individualized treatment strategy has become the core orientation of clinical practice. Current studies have shown that multi-dimensional factors such as tumor anatomical location, stage, molecular characteristics, functional status and willingness to preserve anus should be comprehensively considered in the formulation of treatment plans for LARC. For example, for patients with large tumors or low rectal cancer, consolidation chemotherapy may significantly improve the organ preservation rate by enhancing tumor regression effect. In contrast, for patients at high risk for metastasis (e.g., N2 stage or vascular invasion), induction chemotherapy may improve disease-free survival through early systemic control. In addition, dMMR/MSI-H patients can significantly benefit from neoadjuvant immunotherapy, while MSS patients need to explore the synergistic strategy of radiotherapy combined with immunotherapy. Adaptive treatment adjustment based on dynamic response evaluation (e.g., imaging response, changes in molecular markers), such as the “watch and wait” strategy of adjusting radiotherapy dose according to chemotherapy sensitivity or waiving surgery, further promotes the realization of personalized precision medicine. In the future, the integration of multi-omics data and artificial intelligence prediction models is expected to achieve more refined risk stratification and treatment optimization.

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