

Short-Course Radiotherapy with Delayed Surgery for Locally Advanced Rectal Cancer: Review Article

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ABSTRACT

Multiple studies have found that neoadjuvant long-course concurrent chemoradiotherapy and neoadjuvant short-course radiation therapy with immediate surgical resection have equal efficacy as regards local and distant control. However, PCR was better in long-course radiotherapy. The short-course strategy has decreased the incidence of acute radiation toxicities more than conventional chemoradiotherapy. Short-course radiotherapy is also less expensive plus more practical, particularly in busy oncology centers. There are significant benefits to postponing surgery after preoperative rectal cancer treatment. This concern progresses to the short-course radiotherapy approach with subsequent chemotherapy prior to surgical resection aiming to improve complete pathological response rates with less radiation toxicities. Whether neoadjuvant short-course irradiation with delayed resection or neoadjuvant conventional concurrent chemoradiotherapy is the best strategy is still being debated.

Keywords: Rectal, Preoperative, Radiotherapy, Short course.

INTRODUCTION

Colorectal carcinoma is the 2nd most prevalent reason for cancer death and the third most prevalent tumor in both sexes worldwide. Within Egypt, colorectal cancer ranks seventh among both genders, accounting for 4.2% of the population (9th in men and 8th in women). The median age is 50 years ^(1,2).

Preoperative concurrent chemoradiotherapy with subsequent complete mesorectal excision (TME) within four to eight weeks and preoperative short-course radiation therapy followed by immediate surgical resection after one week were the standard treatments for stages III and II locally advanced rectal cancer. These two approaches demonstrated comparable local and distant control rates, but the long-course approach exhibited higher pathological complete response rates ⁽³⁾. These results led to the development of modern treatment regimens that included a short course of radiotherapy then subsequent chemotherapy and surgical resection postponed for longer than eight weeks.

Standard of neoadjuvant therapy

Due to the high locoregional recurrence risk, neoadjuvant therapy for stage two or stage three rectal cancer should include locoregional treatment. The rectum's proximity to pelvic structures, the serosa absence encircling, and the technical challenges of achieving wide surgical margins during resection all contribute to this risk. Sphincter preservation, local recurrence rate, and radiation-induced toxicities were all improved by neoadjuvant therapy, but regarding 5-year OS, an insignificant difference was found ⁽⁴⁾

Preoperative radiation may have advantages over postoperative radiation in preserving healthy tissue and tumor response. First, decreasing tumor volume may

make surgery easier plus raise sphincter-preserving surgery rates. Secondly, exposing non-surgical tissue, which has a higher concentration of oxygen, to radiation might make it more sensitive to radiation therapy. Thirdly, radiation therapy administered before surgery can shield the small bowel that has been held captive by adhesions in the pelvic region from radiation-induced damage. Preoperative radiation encompassing structures planned for resection enhances the probability of conducting an anastomosis with normal tissue ⁽⁴⁾.

For locally advanced rectal tumors, two neoadjuvant regimens recognized as the neoadjuvant standard therapy were preoperative standard concurrent chemoradiation then operation, and neoadjuvant short-course radiation therapy then subsequent operation after one week ⁽⁴⁾. In numerous studies, both techniques demonstrated comparable long-term survival, late morbidity, and local control. However, long-course RT exhibited higher pathological complete response rates. The acute radiation toxicities associated with the short-course schedule are significantly lower than those associated with conventional CRT. Additionally, in overcrowded oncology centers, short-course irradiation is more practical and financially advantageous ⁽³⁾.

Approximately 50% to sixty percent of cases undergo downstaging following preoperative treatment, while twenty percent exhibit a pathologic complete response ⁽⁴⁾. Recently trials established a correlation between the efficacy of preoperative therapy and the prolonged prognosis in cases diagnosed with rectal tumors. A multivariate analysis of MERCURY trial showed a significant relationship between OS and DFS and the cancer regression level assessed with MRI. Cases with inadequate cancer regression grades showed five-year survival rates of twenty-seven percent compared to

seventy-two percent for cases that showed adequate cancer regression grades, also disease-free survival rates were thirty-one percent compared to sixty-four percent⁽⁵⁾. Cases downstaged to ypT0–2 had a greater probability of gaining advantages from postoperative treatment than cases with ypT3–4 staging, according to the EORTC 22921 study⁽⁶⁾.

Short-course radiotherapy with delayed surgery

Significant benefits are associated with delaying surgical resection for rectal cancer following preoperative treatment: full clinical response potential, additional time for patient optimization, and a decreased postoperative complications risk. However, delaying adjuvant chemotherapy initiation may increase the likelihood of disease progression and deterioration. This concern progresses to the point where the implementation of chemotherapy following short-course radiation therapy prior to surgical resection is considered⁽⁷⁾.

There has been continuous discussion regarding the better regimen: neoadjuvant concurrent chemoradiotherapy or short-course radiotherapy then delayed surgery. Recent studies have evaluated short-course radiotherapy and then consolidation chemotherapy or traditional neoadjuvant long-course radiotherapy administered concurrently with chemotherapy.

In the Polish II trial, participants diagnosed to have locally advanced rectal tumors were randomized to conventional chemo RT strategy or short-course radiation therapy with subsequent chemotherapy, among 515 patients eligible for analysis, 384 ($P=0.006$) experienced a reduction in preoperative acute treatment toxicity in short-course RT. 3-year DFS and local efficacy weren't different; however, the short-course arm exhibited higher three-year overall survival (73 % vs. 65 %, $P=0.046$). Nonetheless, the study's long-term findings established no statistically significant disparity in eight-year OS (49 % for both groups). Comparable late toxicities were observed in two arms⁽⁸⁾.

RAPIDO trial compared long-course chemoradiation therapy prior to surgery for stage T4 or T3 rectal tumor cases to a short-course approach then subsequent chemotherapy. A minimum of 75% of patients finished the prescribed chemotherapy in the experimental group, while only 57% of the conventional group patients achieved this completion level⁽⁹⁾. The long-course arm exhibited a pathologic full response rate of 14 %, while the short-course arm achieved a rate of 28 %. The short-course arm exhibited a reduced three-year disease-related treatment failure rate compared to the long-course group. Additionally, there was a decreased probability of locoregional failure and distant metastasis. In both treatment groups, LAR syndrome score, overall health, and quality of life were comparable. As a result, abstract

reporting patterns of distant recurrence and locoregional failure in the RAPIDO research revealed that the short-course RT arm experienced a greater distant metastases incidence at five years in contrast to the long-course arm (7 % vs. 10 %; HR, 1.50). Thus, caution is advised in this regard when utilizing short-course radiotherapy for high-risk rectal cancer⁽¹⁰⁾.

Stockholm III trial compared short-course and long-course radiation therapy in 840 rectal tumor participants. This study contained two randomizations, A two-arm randomization comparing short-course radiotherapy then immediate surgery to short-course radiotherapy then delayed surgery, and a three-arm randomization comparing short-course radiotherapy then immediate surgery, short-course radiotherapy then delayed surgery, and long-course radiotherapy then delayed surgery. In a three-arm analysis, prevalence of local recurrence was 2.3% for short-course then immediate surgery, 3.1% for short-course then delayed surgery, and 5.4% for long-course RT. For short-course RT then immediate surgery, the median overall survival was 8.1 years; for short-course RT then delayed surgery, 10.3 years; and for long-course RT, it was 10.5 years⁽¹¹⁾.

STELLAR study compares capecitabine-based concurrent chemoradiotherapy with a short-course strategy of radiotherapy and then CAPEOX as preoperative treatment in stage II–III rectal tumors. Adjuvant chemotherapy was given based on preoperative therapy, and the operation was performed six to eight weeks after preoperative therapy in both groups. The three-year DFS for short-course RT was 64.5 %, whereas it was 62.2% for long-course RT. A statistically insignificant difference was shown between the two cohorts regarding distant metastasis or local recurrence. The 3-year overall survival was increased in the short-course RT group; however, the short-course RT group had an increased incidence of acute grade three side effects throughout the neoadjuvant therapy period (26.5 % vs. 12.5 %; $P=0.001$)⁽¹²⁾.

A comprehensive analysis conducted in 2014 identified sixteen pieces of research that examined the duration from short-course RT to rectal tumor operation. Compared to delayed surgery, immediate surgery (1–2 weeks intervals) was associated with a greater minor postoperative complication incidence but a lower incidence of acute post-radiation toxicity (5- to 13-week intervals). The delayed-surgery group exhibited significantly elevated pathologic complete response rates, whereas the R0 resection and sphincter preservation rates were found to be comparable⁽¹³⁾.

In an effort to summarize the current evidence on consolidation chemotherapy after neoadjuvant SCRT prior to surgery, a 2022 meta-analysis and systematic review of approximately 17 studies (retrospective studies,

phase II trials, and RCTs) revealed that this approach improved PCR rates, increased ypN0 stage of initially involved lymph nodes and increased sphincter sparing approach. The increased PCR rate could potentially be ascribed to the extended time between radiation therapy and operation, with the administration of chemotherapy within this time⁽¹⁴⁾.

CONCLUSION

In locally advanced rectal tumor patients, neoadjuvant short-course RT with subsequent chemotherapy is as effective as conventional CRT due to its comparable efficacy and lower toxicity profile in comparison to conventional long-course RT concurrent with chemotherapy. Furthermore, an abbreviated treatment duration offers increased convenience for both patients and physicians, coupled with reduced crowdedness on equipment in overcrowded facilities⁽¹³⁾.

Conflict of interest:

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