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Review

Short-course radiotherapy with immediate or delayed surgery in rectal cancer: A meta-analysis

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ABSTRACT

Background: The safety and efficacy of preoperative short-course radiotherapy had been verified in rectal cancer. However, the timing of surgery after radiation had not been well defined. Thus, we performed this meta-analysis to compare the interval time of surgery after short-course radiotherapy in rectal cancer: immediate surgery (< 4 weeks) vs delayed surgery (> 4 weeks).

Methods: We searched the PubMed, EMBASE, MEDLINE, and Cochrane Library database. The primary endpoints were survival rates and pathological outcomes, and the second endpoints included sphincter preservation rate, R0 resection rate and postoperative complications. RevMan 5.3 was used to calculate pooled risk ratio (RRs) and 95% confidence interval (CIs).

Results: In total, 5 eligible studies including 1244 participants were identified. The delayed surgery group had a markedly higher pathological complete response rate [RR = 15.71, 95% CI (2.10, 117.30), P = 0.007] and downstaging rate [RR = 2.63, 95% CI (1.77, 3.90), P < 0.00001], a higher proportion of patients with adjuvant pathologic stage 0 + I disease [RR = 1.49, 95% CI (1.23, 1.81), P < 0.0001] and a lower incidence of postoperative complications [RR = 0.81, 95% CI (0.70, 0.95), P = 0.008] than did the immediate surgery group, but the survival rate, sphincter preservation rate and R0 resection rate were similar between the two groups.

Conclusion: Based on better pathologic outcomes and fewer postoperative complications, we recommended short-course radiotherapy with delayed surgery for more than 4 weeks.

1. Introduction

Preoperative radiotherapy has been verified as both a safe and an effective strategy for the management of rectal cancer [1–3]. Both short-course radiotherapy and long-course chemoradiation, which are advocated in different parts of the world, are considered optional neoadjuvant strategies with similar survival rates and sphincter preservation rates as confirmed by several randomized controlled trials (RCTs) [4–6]. Short-course radiotherapy with surgery within the following week, which is practiced more in Europe, is less expensive and more convenient, especially in centers with long waiting lists or lack of medical resources, while long-course chemoradiation with delayed surgery, which is preferred in America, markedly increases pathologic complete response (pCR) rates but prolongs the treatment duration [4–7].

Following long-course chemoradiotherapy, a delay of 6–8 weeks before surgery is standard [8]. However, there is a lack of consensus on the timing of surgery after short-course radiotherapy [9]. A retrospective study demonstrated the occurrence of more complications after short-course radiotherapy in rectal cancer patients with longer intervals before surgery beyond 7 days [10]. Conversely, Pettersson D et al., in the interim analysis of Stockholm III trial, reported that patients undergoing short-course radiotherapy with a 4–8 week delay in surgery had fewer postoperative complications than did patients undergoing short-course radiotherapy with immediate surgery within the following week [11,12]. They also demonstrated that short-course radiotherapy led to tumor downstaging if the surgery was performed after 4–8 weeks [13]. Similar conclusions were obtained from two other prospective

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studies comparing different intervals between short-course radiotherapy and surgery [7–14]. Patients undergoing surgery after longer interval demonstrated higher pCR and downstaging rates. Nevertheless, such advantages in pathological outcomes did not translate to improved long-term survival or sphincter preservation rate. Another retrospective study, comparing delayed surgery (> 4 weeks) with immediate surgery (< 4 weeks) after short-course radiotherapy in rectal cancer patients, suggested similar pathological outcomes in the two groups but better overall survival rate in the delayed surgery group [15].

To identify the optimal timing for surgery, we defined immediate surgery and delayed surgery based on an interval of less than and more than four weeks, respectively, between the completion of radiation and surgery [15–18] and conducted this meta-analysis to compare the safety and efficacy between immediate surgery and delayed surgery for the treatment of rectal cancer.

2. Methods

2.1. Literature search

A comprehensive literature search was carried out using PubMed, EMBASE, MEDLINE, and the Cochrane Register of Clinical Trials, using the following search keywords: “surgery or surgical resection or TME or anterior resection or abdominoperineal“ AND ?rectal cancer or rectal carcinoma“ AND ?preoperative or neoadjuvant or radiotherapy or radiation“ AND ?interval or delay or time or timing“ and ”short-course or short-term or 25 Gy” The last search was updated on February 2018. In addition, we reviewed references in the retrieved articles to search for additional relevant studies.

2.2. Inclusion and exclusion criteria

According to the participant, intervention, comparison, outcomes, study design (PICOS) principles, we defined the inclusion criteria as follows: (1) Participants (P): Studies involving patients with rectal cancer confirmed by biopsy. (2) Interventions (I) and comparisons (C): Studies comparing the efficacy and safety between short-course radiotherapy with immediate surgery (SCRT) and short-course radiotherapy with delayed surgery (SCRT-delay) for the management of rectal cancer. The short-course radiotherapy was administered using five fractions of 5 Gy each for a total dose of 25 Gy over 5–7 days. The interval between the completion of radiation and surgery was less than 4 weeks and more than 4 weeks for SCRT and SCRT-delay, respectively. (3) Outcomes (O): Studies evaluating the following outcomes: primary endpoints including overall survival rate (OS), disease-free survival rate (DFS), downstaging rate, pathologic complete response (pCR) rate, adjuvant pathologic stage (ypTNM stage) and second endpoints including sphincter preservation rate, R0 resection rate, postoperative complications. (4) Study design (S): Both prospective and retrospective studies.

The exclusion criteria as follows: (1) Studies involving patients with synchronous metastases; (2) studies that were not controlled trials, such as single arm studies, case series or case reports; (3) studies lacking complete important information for extracting the required data; and (4) non-original studies, such as letters, reviews, and expert opinions.

2.3. Assessment of the risk of bias of included studies

The quality of cohort studies was measured using a scoring system and assessed in accordance with the Newcastle-Ottawa criteria [19]. The total scores ranged from 0 (worst) to 9 (best) for cohort studies, with a score of at least 6 indicative of high quality. The quality of RCTs was assessed using the Cochrane Collaboration's risk for bias assessment tool [20], which evaluates the selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each criterion was assessed as having a low, high, or uncertain risk of bias.

2.4. Data extraction

The following information was extracted from each of the selected papers if available: name of first author, year of publication, type of study, number of patients, demographic characteristics, clinical stage and location of tumor, follow-up duration, intervention and comparison, OS, DFS, pCR rate, downstaging rate, ypTNM stage, sphincter preservation rate, R0 resection rate and postoperative complication. The results were checked by the other authors and discrepancies were settled by consensus.

2.5. Data analysis

All statistical analyses were performed using RevMan 5.3 software. The data were evaluated using pooled risk ratio (RRs) and 95% confidence interval (CIs). Heterogeneity was evaluated by using the I^2 method with the χ^2 test to calculate P values. If heterogeneity was not present ($P > 0.10$, $I^2 < 50\%$), a fixed-effect model was used for analysis; otherwise, a random-effect model was employed.

3. Results

3.1. Study selection

A total of 897 relevant articles were searched, and 412 duplicates were removed. After reviewing the titles and abstracts, 457 of the studies were excluded due to the lack of relevance. Next, 28 full-text articles were further evaluated for eligibility. We excluded another 19 full-text articles – 6 articles for not meeting the criteria for surgery timing and 13 conference abstracts with incomplete data. We excluded 4 more articles because they referred to the same study but with short follow-up durations. Finally, we included five studies with a total of 1244 patients in the meta-analyses (Fig. 1). Two of these studies were RCTs [7,21], and the other three were non-RCTs [14,15,22].

Both RCTs mentioned “randomization” and reported on the generation of an adequate randomized sequence, but only one RCT [21] reported allocation concealment, whereas the other [7] did not. Both 2 RCTs did not mention whether blinding was adopted and the data were complete, however, the limitations mentioned were unlikely to affect the results of quality assessment (Fig. 2 and Fig. 3). The 3 non-RCTs were all cohort studies including one prospective study [14] and two retrospective studies [15,22] with prospectively collected data. All 3 cohort studies scored at least 8 based on the Newcastle-Ottawa criteria (Table 3).

We summarized the characteristics of the five included studies. A total of 1244 patients with rectal cancer, most of which were locally advanced, were assigned to SCRT group (n = 582) or SCRT-delay group (n = 662). The characteristics of studies and patients, showed in Tables 1 and 2, were similar between SCRT group and SCRT-delay group.

3.2. Primary endpoint: survival rates and pathological outcomes

Survival rates including OS and DFS, which were reported in all five studies [7,14,15,21,22], were analyzed (Fig. 4 and Fig. 5). Obvious heterogeneity was observed when evaluating the data regarding OS ($I^2 = 60\%$, $P = 0.04$). Using a random-effect model, we did not detect significant differences between the SCRT-delay and SCRT groups regarding OS [RR = 0.75, 95% CI (0.53, 1.07), P = 0.11]. DFS was also similar between the two groups [RR = 0.78, 95% CI (0.84, 1.14), P = 0.77] and was evaluated using a fixed-effect model owing to the lack of heterogeneity ($I^2 = 0\%$, $P = 0.72$).

Pathological outcomes included pCR rate, downstaging rate and ypTNM stage. Only two trials [7,14] mentioned the pCR rate. Thus, a total of 262 patients were included in this meta-analysis. The RR and 95% CI for each study were summarized in Fig. 6. Compared with that in the SCRT group, the pCR rate was significantly increased in the