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Effect of adjuvant chemotherapy on the oncological outcome of rectal cancer patients with pathological complete response: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 December 2023 and was last updated on 26 December 2023.

INTRODUCTION

Review question / Objective Locally advanced rectal cancer is typically treated using a combination of neoadjuvant chemoradiotherapy and total mesorectal resection. While achieving pathological complete response following neoadjuvant chemoradiotherapy has been recognized as a positive prognostic factor in oncology, the necessity of adjuvant chemotherapy for locally advanced rectal cancer patients with pathological complete response after surgery remains uncertain. The objective of this meta-analysis was to examine the impact of adjuvant chemotherapy on the oncological outcomes of rectal cancer patients who attain pathological complete response after neoadjuvant chemoradiotherapy.

Rationale This meta-analysis followed the guidelines outlined in the preferred reporting items for systematic review and meta-analysis (PRISMA). The Web of Science, PubMed, and Cochrane Library databases were systematically searched to identify relevant literature.

Condition being studied The latest statistics on cancer in 2022 reveal that colorectal cancer (CRC) has emerged as a prominent cancer, ranking third in terms of incidence and second in mortality rates. It is worth noting that the prevalence of CRC is rapidly increasing. Among all CRC cases, approximately 30% are attributed to rectal cancer, with a majority of cases being classified as locally advanced at the time of diagnosis. The standard treatment approach for locally advanced rectal cancer (LARC) involves the utilization of neoadjuvant chemoradiotherapy (NCRT) combined with total mesorectal resection (TME). This treatment strategy offers multiple benefits, such as improved local tumor control, complete tumor removal, and sphincter preservation. However, the

response to NCRT in LARC patients varies considerably.

While a considerable proportion of LARC patients respond positively to NCRT, demonstrating tumor regression, only a relatively small percentage (ranging from 10% to 30% of cases) can achieve a pathological complete response (pCR). The achievement of pCR stands as a crucial milestone, indicating successful tumor eradication and favorable tumor biology. Extensive research has shown that patients who achieve pCR have remarkably low recurrence rates (6-17%) and high 5-year overall survival (OS) rates (87-92.9%). A meta-analysis study revealed that patients with rectal cancer who attain pCR exhibit longer disease-free survival (DFS) and OS than those who don't achieve pCR. Therefore, pCR is increasingly being recognized as a relevant endpoint in the design of clinical trials, acting as a surrogate marker for long-term tumor prognosis.

Adjuvant chemotherapy (ACT) is a commonly employed treatment modality for rectal cancer patients. However, there remains a lack of robust evidence regarding the use of ACT after NCRT and surgery. According to current National Comprehensive Cancer Network (NCCN) guidelines, all NCRT recipients should also undergo 6 months of ACT after surgery, regardless of their pathological regression response. Nevertheless, the impact of ACT on OS and DFS among LARC patients who undergo NCRT is a subject of controversy. Some studies suggest that ACT may promote OS and DFS in LARC, while others contend that it does not affect the oncological prognosis of LARC patients who receive NCRT. It is noteworthy that in several randomized controlled trials (RCTs) involving rectal cancer patients, the choice of postoperative systemic therapy is “at the discretion of the physician”, which contradicts the recommendations provided by the NCCN. Despite the acknowledged prognostic advantage of achieving pCR in oncology, the necessity of ACT for LARC patients who attain pCR after surgery remains uncertain. Based on studies, some scholars argue that ACT improves OS in patients with pCR, while others assert that it may not be necessary for rectal cancer patients with pCR.

METHODS

Search strategy (rectal cancer) and ((neoadjuvant or preoperative) and (chemoradiotherapy or chemoradiation or radiotherapy)) and ((adjuvant or postoperative) and (chemotherapy)) and (pathologic complete).

Participant or population Patients with primary rectal cancer who received neoadjuvant chemoradiotherapy or radiotherapy and achived pathological complete response.

Intervention Adjuvant chemotherapy after surgery.

Comparator Observation after surgery.

Study designs to be included Randomized controlled studies and cohort studies.

Eligibility criteria The exclusion criteria were as follows: (1) local excision or watch-and-wait patients; (2) no desired outcome reported; (3) neoadjuvant chemotherapy only; (4) ypT0 patients with unknown lymph node status; and (5) abstracts, meta-analyses, reviews, comments, and letters.

Information sources Web of Science, PubMed, and Cochrane Library databases.

Main outcome(s) The primary focus was on hazard ratios (HRs) for OS, whereas secondary outcomes involved HRs for DFS and RFS. In addition, the researchers meticulously examined the 5-year rates of OS, DFS, and RFS.

Additional outcome(s) None.

Data management The information was extracted from the full text according to a standardized form. The extracted information included general information such as authors, date of publication, source of data, and time period of the study. Basic clinical characteristics such as age, sex, clinical stage, neoadjuvant radiotherapy regimen, concurrent chemotherapy regimen, interval between last radiation and surgery, surgical modality, adjuvant chemotherapy, and duration of follow-up were also recorded. Oncological outcomes such as OS, DFS, and RFS were also recorded.

Quality assessment / Risk of bias analysis To ensure the reliability and credibility of the retrospective cohort studies, the quality and methodology were assessed using the Newcastle-Ottawa Scale (NOS) score, which encompasses patient selection (4 points), cohort comparability (2 points), and evaluation of exposure or outcome (3 points). A score of 4 to 6 indicates moderate quality, while a score of 7 to 9 indicates high quality. All processes, including data extraction and NOS scoring, were carried out independently by two authors and meticulously cross-checked. In instances of disagreements, a third individual was

consulted, allowing for robust discussions and the eventual attainment of a consensus.

Strategy of data synthesis The data were pooled and analyzed using STATA software (ver. 15; Stata Corp., College Station, TX, USA) and the results were presented using forest plots. Statistical heterogeneity was assessed using the I2 and Cochrane Q tests. If the p value exceeded 0.1 and I2 was below the 50%, it indicated that the heterogeneity was not significant, and a fixed-effect model was employed in this analysis. Conversely, statistical heterogeneity was recognized when the p value was below 0.1 or I2 exceeded 50%, the random-effects model was selected. Sensitivity analyses were conducted to evaluate the reliability of the findings, while subgroup analyses were carried out to identify potential sources of heterogeneity. Funnel plots and Egger's test were utilized to assess publication bias in the analyses of OS, DFS, and RFS. Additionally, adjusted effect sizes were calculated using subtractive complementation if significant publication bias was detected. A statistical significance level of $p<0.05$ was adopted.

Subgroup analysis Subgroup analyses were used to explore age, clinical T-stage, and lymph node status as potential drivers of heterogeneity.

Sensitivity analysis Sensitivity analyses were conducted to evaluate the reliability of the findings, while subgroup analyses were carried out to identify potential sources of heterogeneity.

Language restriction No.

Country(ies) involved China.

Other relevant information None

Keywords rectal cancer, pathological complete response, adjuvant chemotherapy, overall survival.

Contributions of each author

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