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Letter to the Editor

# Adjuvant chemotherapy in patients with rectal cancer achieving pathologic complete response after neoadjuvant chemoradiation and surgery

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The intensification of neoadjuvant therapies (i.e., chemoradiotherapy [CTRT] before surgery has provided a shift in the paradigm of treatment of locally advanced rectal cancer [1]. More recently, despite the short follow-up of published studies [2], the preoperative addition of full doses of induction systemic chemotherapy before CTRT is emerging as a potential new standard of care.

Traditionally, adjuvant chemotherapy is administered after surgery, when there is no clear evidence of residual disease, to increase overall survival (OS), by reducing the risk of distant relapses through the elimination of micrometastatic disease. Whether postoperative chemotherapy adds any benefit to patients who achieve a complete pathologic response (pCR) after surgery and neoadjuvant CTRT is still a matter of debate. Available randomised trials have provided very few conclusive data on this issue. In a meta-analysis of 4 randomised studies, Breugom *et al.* [3] found that adjuvant CT did not improve OS, disease-free survival or distant recurrences in pathological stage II-III (ypTNM stage II-III) after neoadjuvant therapy. In 2014, Maas *et al.* [4] published a pooled analysis of 13 prospective or retrospective cohort studies for a total of 3313 patients with rectal cancer, with the aim of identifying a subgroup of patients who may derive benefit from adjuvant CT. The authors found that only patients with residual tumour after surgery and neoadjuvant CTRT derive a survival benefit from further systemic therapy; conversely, the 898 cases with pCR did not. A further meta-analysis from our group [5] found that a large 5-year OS benefit from adjuvant CT, particularly in those cancers that were downstaged to ypT0-2N0 stage after neoadjuvant CTRT (43% less risk of death). Indeed, this subgroup analysis was explorative and derived from the data of only 5 studies. Recently, two separate observational cohort studies including patients from the US National Cancer Database with locally advanced rectal cancer and pCR after neoadjuvant CTRT and surgery, who were treated with or without adjuvant CT, have been published [6,7]. Both studies used a propensity score matching to reduce the imbalance in patient and treatment characteristics between patients receiving adjuvant CT or postoperative observation only. The authors concluded that adjuvant chemotherapy significantly improves OS with a reduction of the risk of death by 50% and 56% in the 2 studies. However, such results were criticised because of the retrospective nature of the analysis which may have led to an overestimation of treatment effects based on

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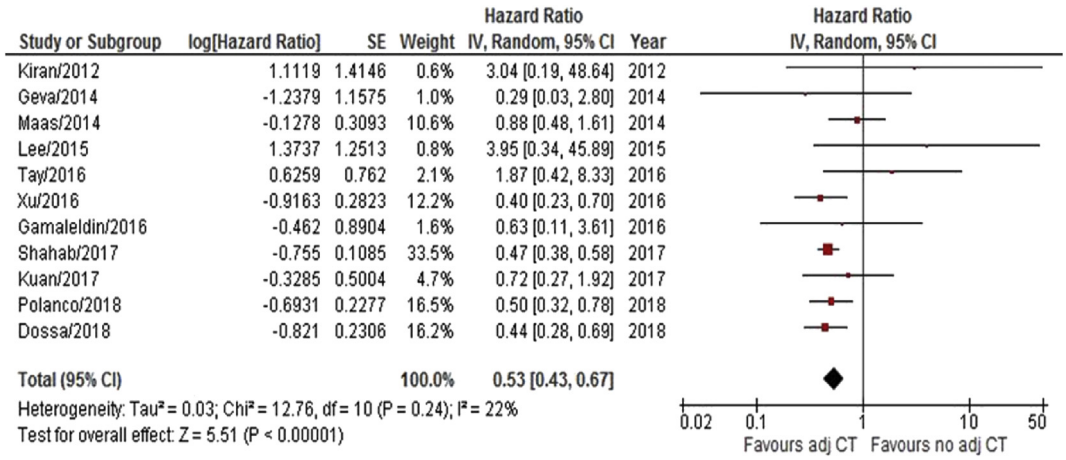


Fig. 1. Overall survival in patients with rectal cancer attaining a pCR and receiving or not adjuvant chemotherapy after surgery. CI, confidence interval; pCR, complete pathologic response; IV, inverse variance; SE, standard error.

unassessed factors and because approximately 70% of the patients in each cohort did not receive any adjuvant chemotherapy, suggesting the possible risk of selection bias.

Therefore, we performed a meta-analysis of all available adjuvant CT series reporting data of patients with rectal cancer and pCR and receiving or not adjuvant CT after surgery and neoadjuvant treatment. Studies were selected based on the following inclusion criteria: (1) randomised trials, cohort and retrospective studies were considered; (2) patients with rectal cancer treated with neoadjuvant CTRT and surgery, and achieving a pCR defined as ypT0N0 stage; (3) the study compared adjuvant CT or observation after radical surgery; (4) the study should provide hazard ratio (HR) or survival curves of OS and (5) the study was published in English language. A total of 11 publications consisting of a total of 9083 patients were included. Our analysis revealed that adjuvant CT significantly improved OS in patients with pCR (HR = 0.50, 95% confidence interval [CI] 0.43–0.59; $p < 0.001$; Fig. 1) [6,8–10,10–16]. The fixed-effects model was used for the analysis because of low heterogeneity ($I^2 = 22\%$) between the trials. After performing the analysis based on the random-effects model, the final result did not change (HR = 0.53, 95% CI 0.43–0.67; $p < 0.001$).

Findings from this meta-analysis strengthen the concept that subjects treated for rectal cancer and staged as ypT0N0 after surgery should receive 5-fluorouracil–based adjuvant CT. Although these results derive from a literature-based rather than an individual patient data meta-analysis, we believe that the effects of adjuvant CT are remarkable, resulting in a 50% reduced risk of death. further larger prospective confirmatory studies, specifically designed for this highly favourable prognostic group of patients and incorporating adequate translational research parts, are necessary.

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## Conflict of interest statement

None declared.

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