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Review

Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin

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Abstract

Background: There is no consensus on the role of postoperative chemotherapy in patients with rectal cancer who have received preoperative radio(chemo)therapy.
Materials and methods: A systematic review and meta-analysis were performed of trials that used preoperative radio(chemo)therapy and randomized patients either between postoperative chemotherapy and observation or between a fluoropyrimidine only (FU-only) and a fluoropyrimidine with oxaliplatin (FU−OXA) as postoperative chemotherapy.
Results: Five randomized studies compared postoperative chemotherapy with observation in a total of 2398 patients. None of these trials demonstrated a statistically significant benefit of chemotherapy for OS and DFS. The pooled differences in OS and DFS did not differ statistically significantly between the chemotherapy group and the observation group. The hazard ratios (HRs) and 95% confidence intervals (CIs) were 0.95 (CI: 0.82−1.10), $P = 0.49$ and 0.92 (CI: 0.80−1.04), $P = 0.19$, respectively. In the subgroup of trials in which randomization was performed after surgery (n = 753), a statistically significant positive pooled chemotherapy effect was observed for DFS (HR = 0.79, 95% CI: 0.62−1.00, $P = 0.047$), but not for OS ($P = 0.39$). Four randomized trials compared adjuvant FU−OXA with adjuvant FU-only in 2710 patients. In two trials, the difference in DFS between groups was statistically significant in favour of FU−OXA, and in the other two trials, the difference was not significant. The pooled difference in DFS between the FU−OXA group and the FU-only group was not statistically significant: HR = 0.84 (CI: 0.66−1.06), $P = 0.15$.
Conclusion: The use of postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy is not based on strong scientific evidence.

Keywords: Rectal cancer; Adjuvant chemotherapy; Oxaliplatin-combination

Introduction

There is variability in the recommendations for postoperative chemotherapy in patients with rectal cancer who have already received preoperative radiotherapy of radiochemotherapy. The National Comprehensive Cancer

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Network (NCCN) guidelines recommend after preoperative chemoradiotherapy and surgery postoperative adjuvant chemotherapy for patients with clinical stage II and III disease regardless of the surgical pathology results.[1] By contrast, the European Society for Medical Oncology (ESMO) recommendations state, "As in colon cancer stage III (and "high risk" stage II), adjuvant chemotherapy can be given, …".[2] In contrast to the ESMO guidelines, Dutch and Norwegian guidelines do not recommend postoperative chemotherapy in patients who have received preoperative radio(chemo)therapy.[3] These inconsistencies in guidelines are reflected in clinical practice. In an analysis of the Surveillance, Epidemiology, and End Results Medicare Data, more than one in three patients treated between 1998 and 2007 did not receive adjuvant chemotherapy.[4] Contrary to the NCCN recommendations,[1] the use of postoperative chemotherapy in this study was also influenced by surgical pathology findings. A population-based Swedish study has shown that the use of adjuvant chemotherapy for stage III rectal cancer ranged from 13% to 77% in different counties.[5] This variability is also reflected in the lack of consensus between European experts.[6]

The aim of the current investigation was to evaluate whether scientific evidence supports the use of adjuvant chemotherapy in patients who have already received preoperative radio(chemo)therapy. Building upon previous searches,[7,8] this meta-analysis was performed to examine the evidence from randomized studies. An update was necessary because updated results from two large, previously reported trials and the first results from two other trials, which included a surgery-only group, became available in 2014. Several trials exploring the value of adding oxaliplatin (OXA) to a fluoropyrimidine (FU) have also been reported recently, and this topic has not previously been examined in a meta-analysis.

Material and methods

The studies qualified for the current review if they (i) included patients with rectal adenocarcinoma having received preoperative radio(chemo)therapy and (ii) randomized the patients either between postoperative chemotherapy and observation or between FU-only and FU plus OXA (FU–OXA) as postoperative chemotherapy.

A literature search was performed of the PubMed and Cochrane Library databases and the abstracts of the American Society of Clinical Oncology, the European Cancer Care Organization, the ESMO meetings and the Word Colorectal Cancer Congress in Barcelona. The titles and abstracts were searched electronically from May 2011 (the limit of a previous review)[8] through March 2015 independently by two authors. The search was without any language restrictions, used "randomized controlled trials" as a limit, and was performed using the free keywords "rectal cancer chemotherapy" or "colorectal cancer chemotherapy". The search was supplemented with the "related articles" function, hand searches of reference lists of all available review articles, meta-analyses, original studies and handbooks. Full text copies of all studies were obtained, and the relevant data were extracted independently by two investigators using a data-collection form. The trials were evaluated using Cochrane Collaboration's tool for assessing the risk of bias.[9] Inconsistencies were resolved by consensus.

The meta-analysis was performed using the Metafor package of R software.[10] Intention-to-treat principle was used. If available, originally published hazard ratios (HRs) and their 95% confidence intervals (CIs) were used to calculate a summary effect using the method described by Parmar et al.[11] If the HR was not available, relative risks and their 95% CIs were calculated based on the numbers of events and patients. It was assumed that the relative risk represents an approximation of HR. A random-effect model was used to create the pooled effect for efficacy. Weighting was based on sample size only. The significance of heterogeneity was tested using Cochrane's Q chi-square test. The absolute differences in 5-year survival between the randomized groups were calculated using the equations: $D = Se - Sc$ and $Se = Sc^r$, where D is the difference in 5-year survival between groups, Se is survival at 5 years in the experimental group, Sc is survival at 5 years in the control group, and r is the HR.[12]

Results

Of the 881 records identified through database searching, screening of the titles resulted in the exclusion of 840 irrelevant or duplicate publications. Of the 41 abstracts or full-text articles assessed for eligibility, 11 publications of eight randomized relevant trials were found[13–23]; three of these reports described updated results of two previously published trials. Including one trial[24,25] found in the previous reviews,[7,8] nine trials in total were eligible.

The evaluation of the risk of bias in the included trials addressed seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and "other issues". Of the nine trials included, seven were assigned to the low risk of bias category, and the other two[19,23] to the unclear risk of bias category because of inadequate information (published as abstracts).

The percentage of randomized patients starting with adjuvant chemotherapy ranged from 63% to 95% (Tables 1 and 2). Timing of randomization was the main reason for this large range. In the trials in which randomization was performed before the preoperative radio(chemo)therapy,[13,15,20] the percentage of patients starting chemotherapy was lower than in the trials in which randomization was performed after surgery[16,17,22]; 63%–78% vs. 92%–95%, respectively. Of patients who started postoperative chemotherapy, the percentage of those who received full

Table 1
Randomized trials in which adjuvant chemotherapy has been explored in patients with rectal cancer receiving preoperative radio(chemo)therapy.

Study	Patients	Design	Results	Comments
EORTC 22921[12,13]	1011 patients with cT3−4 tumours. Accrual 1993−2003.	2 × 2 factorial randomization to preoperative radiotherapy alone vs. preoperative radiochemotherapy (radiation with bolus FU and LV) and to postoperative chemotherapy (4 cycles of FU 50 mg/m^2 and LV 20 mg/m^2 on days 1−5 every 21 days) vs. no postoperative chemotherapy.	Median follow-up 10.4 years. 10-year OS 51.8% in the postoperative chemotherapy group and 48.4% in the control group, HR = 0.91 (CI 0.77−1.09), $P = 0.32$; 10-year DFS 47.0% in the postoperative chemotherapy group and 43.7% in the control group, HR = 0.91 (CI 0.77−1.08), $P = 0.29$. In 787 patients without distant metastases before or at surgery and who had R0 resection HR = 0.96 (CI 0.78−1.19) for OS and HR = 0.98 (CI 0.81−1.20) for DFS.	Randomization before radio(chemo)therapy. No statistically significant benefit of adjuvant chemotherapy regardless of if patients had been given preoperative chemoradiation or preoperative radiation alone. 73% of patients started chemotherapy; of these 59% received full dose. Short postoperative chemotherapy − only 12 weeks.
Italian trial[14]	634 patients with clinically staged II−III tumours. All patients had preoperative radiochemotherapy (bolus FU and LV). Accrual 1991−2001.	Randomization to postoperative chemotherapy (6 cycles of bolus FU 325 mg/m^2 and LV 20 mg/m^2 on days 1−5 every 28 days) vs. no postoperative chemotherapy.	Median follow-up 5.3 years. 5-year OS 66.9% in the postoperative chemotherapy group and 67.9% in the control group, $P = 0.88$. 5-year DFS 63.6% and 60.8%, respectively, $P = 0.42$. In the chemotherapy group OS at 5 years 69.2% for those receiving ≥3 cycles of postoperative chemotherapy vs. 68.9% for those receiving <3 cycles.	Randomization before radiochemotherapy. Only reported as an abstract. Of patients who had tumour resected, 63% started chemotherapy and of these 21% received less than 3 cycles.
PROCTOR/SCRIPT study[15]	437 patients with ypStage II or III after preoperative radiochemotherapy or 5 × 5 Gy. Accrual 2000−2013.	Randomization to postoperative chemotherapy (FU and LV according to the Mayo or Nordic regimen or 8 cycles of capecitabine 1250 mg/m^2 twice daily on days 1−14) for 6 months vs. no postoperative chemotherapy.	Median follow-up 5 years. 5-year OS 80.4% in the chemotherapy group and 79.2% in the control group, HR = 0.93 (CI 0.62−1.39), $P = 0.73$. 5-year DFS 62.7% in the chemotherapy group and 55.4% in the control group, HR 0.80 (CI 0.02−1.07), $P = 0.13$. 5-year cumulative incidence for local recurrence was 7.8% in both groups and for distant recurrences 34.7% and 38.5%, respectively, $P = 0.39$	Randomization after surgery. Closed prematurely because of poor accrual. 95.4% of patients started chemotherapy. Compliance to all planned cycles of chemotherapy 73.6%.
CHRONICLE study[16]	113 patients with ypStage 0−III, R0 resection after fluoropirimidine-based radiochemotherapy. Accrual 2004−2008.	Randomization to postoperative chemotherapy (6 cycles of capecitabine 1000 mg/m^2 twice daily on days 1−14 and oxaliplatin 130 mg/m^2 on day 1 every 21 days) vs. no postoperative chemotherapy.	Median follow-up 3.6 years. 3-year OS 89% in the chemotherapy group and 88% in the control group, HR = 1.18 (CI 0.43−3.26), $P = 0.75$. 3-year DFS 78% in the chemotherapy group and 71% in the control group, HR = 0.80 (CI 0.38−1.69), $P = 0.56$.	Randomization after surgery. Closed prematurely because of poor accrual. Grade III + toxicity observed in 40% of the patients.

(*continued on next page*)

Table 1 (*continued*)

Study	Patients	Design	Results	Comments
QUASAR study[23,24]	Uncertain indication for chemotherapy (mostly ypStage II). Colon (2291 patients) and rectal (948 patients) cancer. Accrual 1993–2003. Of rectal cancer patients 203 eligible patients (21.4%) had preoperative radiotherapy and 264 (27.8%) had postoperative radiotherapy. For patients receiving preoperative radiation, the schedule of radiation and clinical and pathological stages were not given.	Randomization to postoperative chemotherapy (6 cycles or 30 once-weekly cycles of FU 370 mg/m^2 on days 1–5 every 4 weeks and high- or low-dose LV, some patients also received levamisol) vs. no postoperative chemotherapy.	Median follow-up 5.5 years. Results for all rectal cancer patients; 5-year OS 78% in the postoperative chemotherapy group and 74% in the control group, HR 0.77 (CI 0.54–1.00), $P = 0.05$; HR for recurrence 0.68 (CI 0.52–0.88), $P = 0.004$. The benefit of chemotherapy was similar in rectal and colon cancers. Also similar irrespective of whether patients were given preoperative radiation, postoperative radiation or no radiation; heterogeneity between groups: $P = 0.30$ for OS and $P = 0.76$ for recurrence. For the preoperative radiation subgroup the benefit was statistically not significant: odds ratio of death 0.44 (CI 0.25–1.10); odds ratio of recurrence 0.55 (CI 0.23–1.20).	Randomization after surgery. Small sample size of the preoperative radiotherapy group (N = 203). Adherence to postoperative chemotherapy in this subgroup was not given.

Abbreviations used: FU – 5-fluorouracil; LV – leucovorin, CI – 95% confidence interval, HR – hazard ratio, OS – overall survival, DFS – disease-free survival.

chemotherapy doses was similar in the two groups according to time of randomization and ranged from 39% to 68% (Tables 1 and 2).

Randomized trials using a control group without postoperative chemotherapy

Description of the trials

Five randomized studies compared postoperative chemotherapy with observation in patients given preoperative radio(chemo)therapy (Table 1). These trials entered a total of 2398 patients. Four studies, EORTC 22921,[13,14] Italian,[15] PROCTOR/SCRIPT,[16] and QUASAR,[24,25] used FU-only schedules, and the fifth study, CHRONICLE,[17] used FU–OXA.

In three of the trials, postoperative chemotherapy was given regardless of the tumour response to the preoperative radio(chemo)therapy. In the other two trials, postoperative chemotherapy was scheduled only for patients with ypStage II–III disease. The QUASAR trial[24,25] explored the value of adjuvant chemotherapy in colon or rectal cancer patients treated with surgery alone or with pre- or postoperative radiotherapy; the current meta-analysis included only patients given preoperative radiotherapy for rectal cancer. Only patients whose tumour had been radically resected were included in the analyses of the trials that used randomization before the preoperative radio(chemo) therapy.[13,15]

Effects on overall survival (OS) and disease-free survival (DFS)

None of the trials demonstrated a statistically significant benefit of chemotherapy for OS or DFS (Table 1, Fig. 1). The difference in OS between patients receiving postoperative chemotherapy and those observed was not statistically significant (HR = 0.95, 95% CI: 0.82–1.10, $P = 0.49$) when the results of all trials were put together (Fig. 1A). This HR translates to a 1.3% absolute difference in 5-year OS in favour of postoperative chemotherapy assuming a 70% OS rate at 5 years in the control group. The difference in DFS between patients randomized to postoperative chemotherapy and those observed was also not statistically significant (HR = 0.92, 95% CI: 0.80–1.04, $P = 0.19$) (Fig. 1B). This HR translates to a 2.5% absolute difference in 5-year DFS in favour of postoperative chemotherapy, assuming a 60% DFS rate at 5 years in the control group.

In the subgroup of trials in which randomization was performed after surgery (n = 753), a statistically significant positive pooled chemotherapy effect was observed for DFS (HR = 0.79, 95% CI: 0.62–1.00, $P = 0.047$), but not for OS ($P = 0.39$) (Fig. 1). In the subgroup of trials in which randomization was performed before the preoperative

Table 2
Randomized trials in which adjuvant oxaliplatin plus fluoropyrimidine postoperative chemotherapy was compared to fluoropyrimidine-only postoperative chemotherapy in patients with rectal cancer who have received preoperative radio(chemo)therapy.

Study	Patients	Design	Results	Comments
PETACC-6 study[17,18]	1069 patients with clinical stage II–III. Accrual 2008–2011.	Randomization to preoperative capecitabine (capecitabine 825 mg/m^2 twice daily) chemoradiation with 6 cycles of postoperative capecitabine (capecitabine 1000 mg/m^2 twice daily on days 1–15 every three weeks) or to receive the same regimen with the addition of oxaliplatin before (oxaliplatin 50 mg/m^2 on days 1, 8, 15, 22, 29) and after surgery (oxaliplatin 130 mg/m^2 on day 1 every three weeks).	Median follow-up 31 months. 3-year DFS 73.9% in the CAPOX group and 74.5% in the capecitabine group, HR = 1.04 (CI 0.81–1.33), $P = 0.781$.	Randomization before radiochemotherapy. Adherence to postoperative chemotherapy was not given. The trial has been reported only as abstract.
CAO/ARO/AIO-04 study[19,20]	1265 patients with clinical stage II–III. Accrual 2006–2010.	Randomization to preoperative FU radiochemotherapy (infused FU 1 g/m^2 on days 1–5 and 29–33) with postoperative 4 cycles of bolus FU (FU 500 mg/m^2 on days 1–5 every 4 weeks) or to preoperative FOLFOX radiochemotherapy (infused FU 250 mg/m^2 on days 1–14 and 22–35, oxaliplatin 50 mg/m^2 on days 1, 8, 22, 29) with postoperative 8 cycles of FOLFOX (oxaliplatin 100 mg/m^2 on day 1, infused FU 2400 mg/m^2 on days 1–2, LV 400 mg/m^2 on day 1 every 2 weeks).	Median follow-up 50 months. 3-year DFS 75.9% in the FOLFOX group and 71.2% in the FU group, HR = 0.79 (CI 0.64–0.98), $P = 0.03$.	Randomization before radiochemotherapy. The FU chemotherapy differed between the two randomized groups both when given simultaneously with radiation and as postoperative treatment. 78% of patients in both groups started postoperative chemotherapy. Of these 81% received all planned cycles in the FOLFOX group and 83% in the FU group; the full dose was given in 44% and 45% of patients, respectively. DFS has been reported only in abstract.
ADORE study[21]	321 patients with pathological II–III stage. Accrual 2008–2012.	Radiochemotherapy with fluoropyrimidines alone. Randomization to postoperative chemotherapy with 4 cycles of FU/LV (FU 380 mg/m^2, LV 20 mg/m^2 on days 1–5 every 4 weeks) or 8 cycles of FOLFOX (oxaliplatin 85 mg/m^2, LV 200 mg/m^2, FU bolus 400 mg/m^2 on day 1, FU infusion 2400 mg/m^2 for 46 h every 2 weeks).	Median follow-up 38 months. 3-year DFS 71.6% in the FOLFOX group and 62.9% in the FU/LV group, HR = 0.66 (CI 0.43–0.99), $P = 0.047$. 3-year OS 95.0% and 85.7%, respectively, HR = 0.46 (CI 0.22–0.97), $P = 0.036$. In the subgroup analyses, the difference in DFS was statistically significant for ypStage III and not significant for ypStage II.	Randomization after surgery. Small sample size. Postoperative FU differed between groups. Grade 3–4 adverse events statistically not different between groups. 92% of patients started chemotherapy. Of these 95% of patients in the 5-FU/LV group and 97% in the FOLFOX group completed all planned cycles of postoperative chemotherapy; the full dose was given in 68% and 39% of patients, respectively.
ECOG E3201 study[22]	55 patients with stage II–III cancer after preoperative FU-based radiochemotherapy.	Randomization to FOLFOX or 5-FU/LV, 8 cycles. Chemotherapy doses were not reported.	Median follow-up 7.4 years. 5 year OS identical – 83% in both groups.	Small sample size. Closed prematurely because of development of an alternative trial with bevacizumab. It is uncertain whether randomization was carried out in clinical stage II–III before radiochemotherapy or in ypStage II–III after surgery. The trial has been reported only as abstract. Adherence to postoperative chemotherapy was not given.

Abbreviations used: FU – 5-fluorouracil; LV – leucovorin, CI – 95% confidence interval, HR – hazard ratio, OS – overall survival, DFS – disease-free survival.

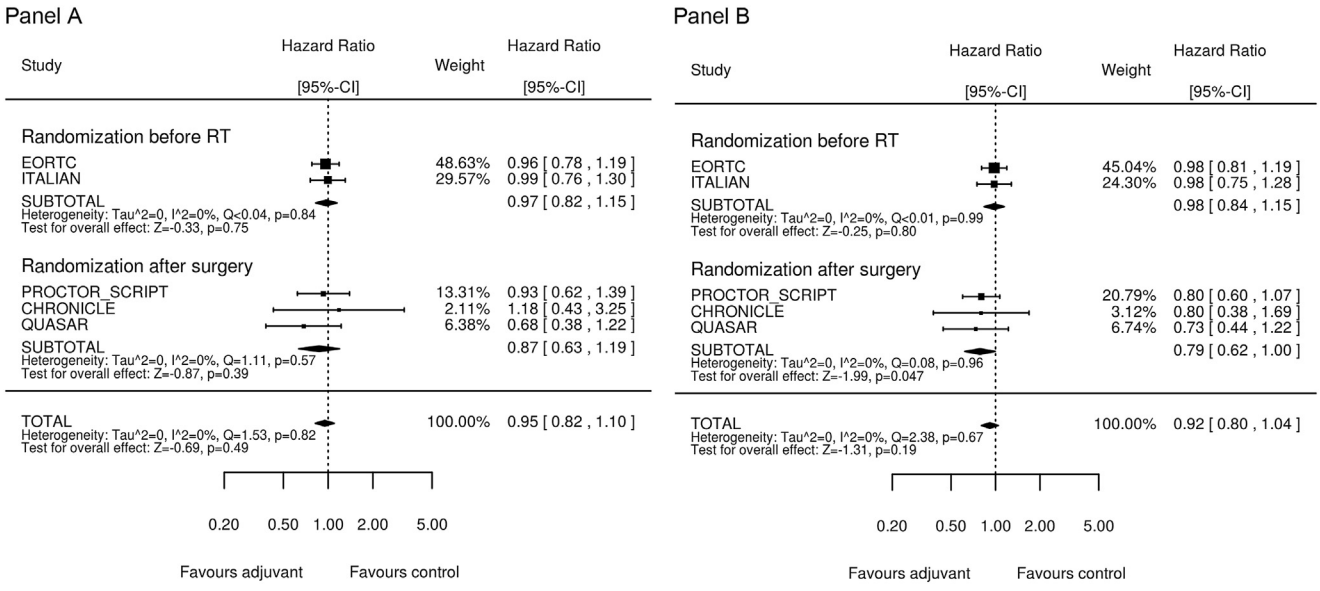

Figure 1. Forest plot of the comparison of postoperative chemotherapy with observation in rectal cancer patients having received preoperative radio(chemo) therapy. Hazard ratio (HR) of death (panel A) and HR of recurrence or death (panel B). Footnote: For the EORTC and QUASAR trials, the forest plots show the relative risk as an approximation of the HR.

radio(chemo)therapy (n = 1645), no chemotherapy effect was observed for OS and DFS (Fig. 1).

Subgroup analyses

A separate meta-analysis was performed for patients with tumours downstaged after radio(chemo)therapy to ypT0–2 because it is believed that the same tumour biological factors may influence both tumour cell sensitivity to the preoperative treatment and benefits from adjuvant chemotherapy. A meta-analysis was also performed for ypStage III patients because the largest benefit in survival from adjuvant chemotherapy in colon cancer was found in this subgroup. Only the EORTC study and the Italian study provided relevant information. The differences in OS and DFS between patients receiving postoperative chemotherapy and those observed was not statistically significant in the ypT0–2 subgroup (n = 745) (Fig. 2). In this subgroup, the HRs were 0.96 (95% CI: 0.75–1.23), $P = 0.75$ for OS and 0.95 (95% CI: 0.73–1.23), $P = 0.71$ for DFS. In the ypStage III subgroup ($n = 365$), the HRs were 1.02 (95% CI: 0.81–1.29), $P = 0.84$ for OS and 1.03 (95% CI: 0.83–1.27), $P = 0.81$ for DFS (Fig. 2).

Evidence of therapeutic effect of adding oxaliplatin (OXA) to a fluoropyrimidine (FU) in postoperative chemotherapy

Table 2 and Fig. 3 summarize the results of the four randomized trials in which adjuvant FU–OXA chemotherapy was compared with adjuvant FU-only in patients given preoperative radiochemotherapy.[18–23] The trials entered a total of 2710 patients. Three of these trials have published survival data in abstract form only. Three trials have a short observation time and DFS as the main endpoint.

Of the two largest trials, the CAO/ARO/AIO-04 study[20,21] showed a statistically significant DFS benefit with the addition of OXA, whereas the PETACC-6 study[18,19] did not. In both trials, randomization was performed before the preoperative radiochemotherapy. Postoperative chemotherapy was given regardless of the response to radiochemotherapy, and OXA was added to both the preoperative radiochemotherapy and the postoperative chemotherapy.

A small Korean study (ADORE), planned as a randomized phase II trial, showed a statistically significantly better DFS in the FU–OXA group compared with the FU-only group.[22] This trial has some merits. Randomization was performed only in high-risk patients (ypStage II–III), and the current standard of preoperative radiochemotherapy (FU-only) was used. However, there was a difference in postoperative delivery of 5-FU in the two arms (Table 2). A fourth trial, the ECOG E3201 study, was terminated prematurely and included only 55 patients who received preoperative radiochemotherapy.[23] No benefit for OS from adding OXA was found (Table 2). The ECOG E3201 study was excluded from the calculation of a summary effect because the abstract did not contain relevant information.

A meta-analysis was possible using DFS as an endpoint. The difference in DFS between patients receiving FU–OXA postoperative chemotherapy and those receiving FU-only was not statistically significant (HR = 0.84, 95% CI: 0.66–1.06, $P = 0.15$). This HR translates to a 5.1% absolute difference in 5-year DFS in favour of FU–OXA assuming a 60% DFS rate at 5 years in the FU-only group.

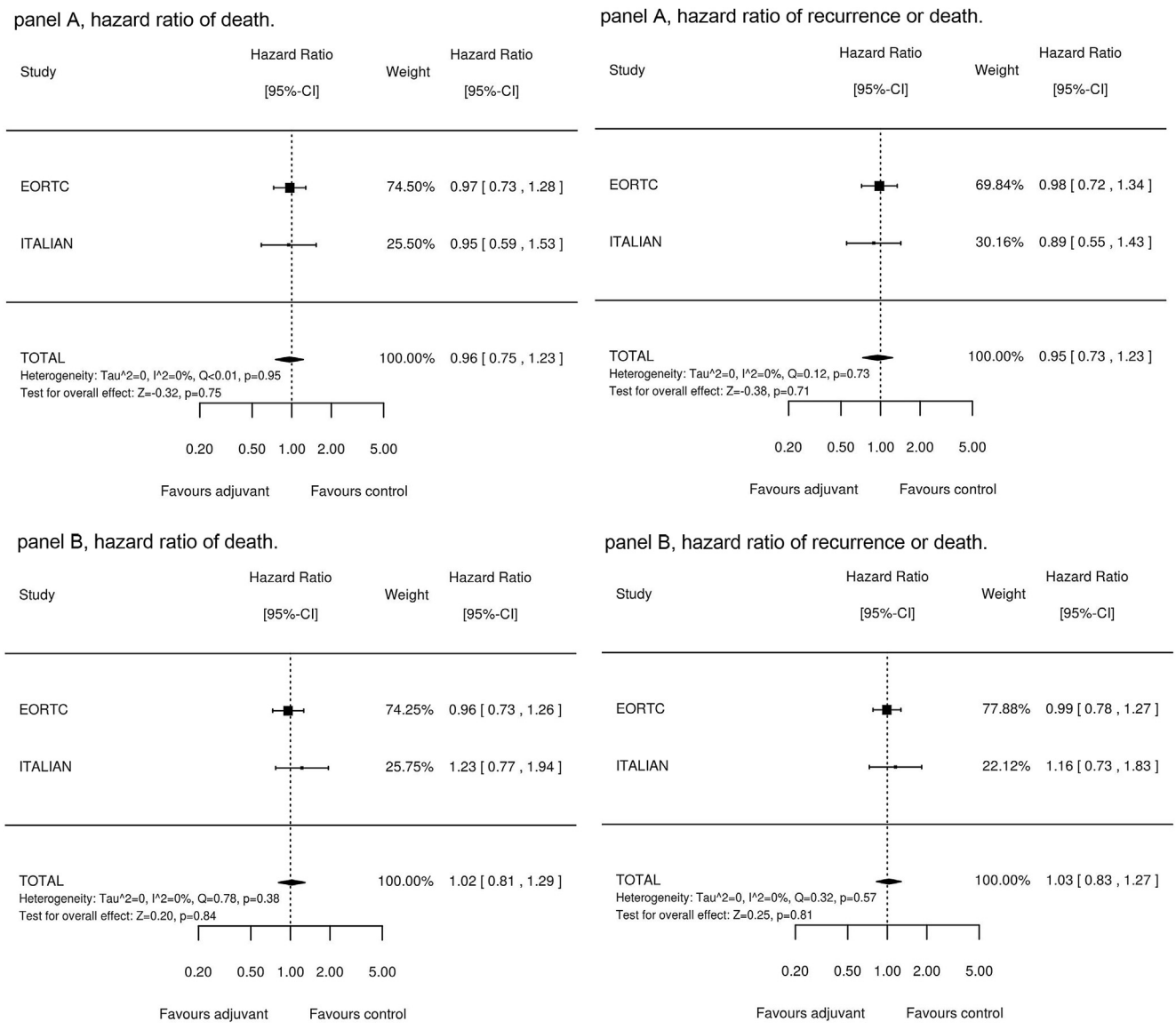

Figure 2. Forest plot of the comparison of postoperative chemotherapy with observation in rectal cancer patients having received preoperative radio(chemo) therapy. Analyses in the ypT0–2 subgroup (panel A) and in the ypStage III subgroup (panel B). Footnote: For the EORTC trial, the forest plot shows relative risk as an approximation of the hazard ratio (HR).

Discussion

The improvement in local control obtained by adding pre- or postoperative radio(chemo)therapy in two recent trials has not translated into a benefit in OS.[13,26] The rate of distant metastases has been shown consistently to be about 30% for clinically staged T3 disease.[13,26] Thus, the need for effective postoperative chemotherapy is definitive.

This meta-analysis demonstrates that the survival differences between patients who received postoperative chemotherapy and those who did not in an observation group were not statistically significant (Fig. 1). The current meta-analysis used data extracted from the literature. Meta-analyses of individual patient data assure lower risks of bias and enable analyses in subgroups. Such a meta-analysis of four randomized trials,[13,15–17] all included in the current meta-analysis, that compared adjuvant chemotherapy with observation in patients given preoperative radiotherapy was recently published by Breugom et al.[27] The median follow-up was 7.0 years. The QUASAR trial and patients with ypTNM-stage I or with R1 resection were excluded from that meta-analysis, whereas they were not from the current meta-analysis. In spite of these differences, the estimations of the pooled effects of adjuvant chemotherapy were almost identical. HRs for OS were 0.97 (95% CI 0.81–1.17) in the Breugom et al.[27] meta-analysis and 0.95 (95% CI 0.82–1.10) in the current meta-analysis; HRs for DFS were 0.91 (95% CI 0.77–1.07) and 0.92 (CI: 0.80–1.04), respectively. In subgroup analyses of the Breugom et al.[27] meta-analysis, patients with a tumour 10–15 cm from the anal verge had improved DFS (HR = 0.59, 95% CI 0.40–0.85, P = 0.005,

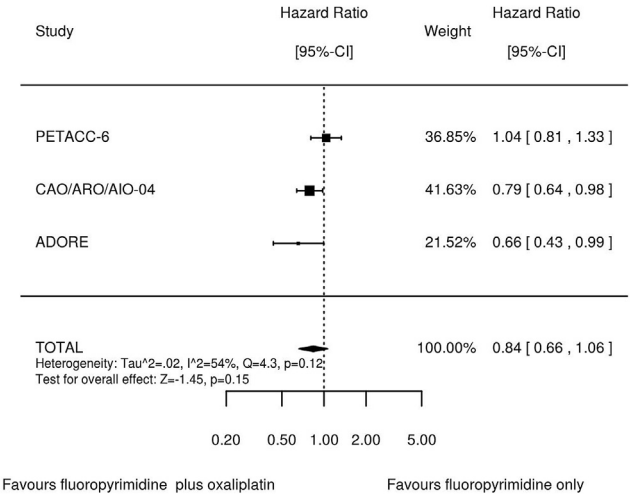

Figure 3. Forest plot of the comparison between postoperative oxaliplatin-containing chemotherapy and postoperative fluoropyrimidine-only chemotherapy in patients with rectal cancer who have received preoperative radiochemotherapy. Hazard ratio of recurrence or death.

$P_{interaction} = 0.107$), but not OS. For all other subgroups analysed (ypTNM-stage II vs stage III, anterior resection vs abdominoperineal resection, ypN0 vs ypN1 vs ypN2, short-course radiotherapy vs long-course radiotherapy vs long-course chemoradiotherapy) no significant differences were detected between observation and adjuvant chemotherapy, neither in OS nor in DFS. The current meta-analysis also showed that there were no differences in OS and DFS between the two groups in the ypT0–2 subgroup (Fig. 2).

The current meta-analysis is the only one published thus far that has compared patients with rectal cancer given preoperative chemoradiation who received FU-only with those who received combination chemotherapy (FU–OXA) postoperatively. The pooled difference in DFS between the two groups was not statistically significant (Fig. 3). Thus, the body of evidence from randomized trials does not show that postoperative chemotherapy improves survival in patients with rectal cancer who have received preoperative radio(chemo)therapy. Therefore, the use of postoperative chemotherapy in these patients does not rely on strong scientific evidence.

Limitations of the current meta-analyses should be acknowledged. Differences in the trials' design were noted that hamper interpretation of the pooled effects of postoperative chemotherapy. Randomization was performed either before the preoperative radio(chemo)therapy or after surgery. In the first setting, many patients randomized to postoperative chemotherapy did not start this treatment because of no tumour resection, postoperative complications, disease progression, patient refusal or toxicity of the preoperative treatment.[28] For obvious reasons, the above mentioned patients were not appropriate candidates for postoperative chemotherapy but excluding them would introduce severe bias, violating the intention-to-treat principle. Therefore, randomization before the preoperative therapy is suboptimal because it diminishes the possibilities to detect an effect from postoperative chemotherapy, if true. Indeed, in the trials in which randomization was performed after surgery, a statistically significant positive pooled chemotherapy effect was observed for DFS, but not for OS (Fig. 1). Better effectiveness of postoperative chemotherapy in the trials in which randomization was performed after surgery may be also related to the use of oxaliplatin and/or capecitabine in the CHRONICLE[17] and PROCTOR/SCRIPT[16] studies. The two trials in which randomization was performed before the preoperative radio(chemo) therapy used 5-Fu and leucovorin as adjuvant therapy. The trials extend over a period of 20 years. Surgical techniques and selection for radiotherapy have changed markedly in this period. Thus the old trials may not be relevant for the current situation. Some trials do not explicitly explain whether the selection of patients is based on tumour at the margin or within 1 mm of the margin; this may also introduce heterogeneity between studies.

Three of the nine trials included in this review were published in abstract form only. This confers lack of peer review and means that limited data is available. However, this also means that the meta-analysis is updated.

The results of the current meta-analysis are consistent with a previous systematic overview,[7] which found no survival benefit from postoperative chemotherapy in patients receiving preoperative radio(chemo)therapy, as reported here, and in seven randomized trials, which were not included in the current meta-analysis because they did not meet the entry criteria; in these trials the patients were given postoperative radio(chemo)therapy or a substantial number received pre- or postoperative radiation.

Extrapolation of findings from colon cancer, for which survival benefit from postoperative chemotherapy has been clearly shown, is used to justify the use of postoperative chemotherapy for rectal cancer patients whether given preoperative radio(chemo)therapy or not. There are no major differences in the genetics or in the response to palliative chemotherapy between the cancers at these two sites. However, in contrast to patients with colon cancer, patients with rectal cancer often receive preoperative radiotherapy, and these patients have a higher incidence of at least symptomatic local recurrences. In extraperitoneal rectal cancer, the internal iliac and obturator regional lymph nodes, which may contain metastases, are not resected, and distant metastases occur more often in the lungs and less often in the peritoneum compared with colon and intraperitoneal rectal cancers.[29–31] However, the lateral lymph nodes are frequently within the irradiated tumour target volume if radio(chemo)therapy is given.

In the analyses of the subgroup of patients with a pathological complete response (pCR) or in ypT1-2 (indicating a major effect of the preoperative radio(chemo)therapy), no effect of postoperative chemotherapy was found (Fig. 2). Moreover, the risk of relapse in those patients is well below

20%.[32–37] Thus with the use of postoperative chemotherapy in this subgroup, overtreatment is expected to be very high. However, the results in the ypT0-2 subgroup should be interpreted with caution because the pooled effects were calculated for small sample sizes from unplanned subgroup analyses of two trials with the suboptimal methodology (randomization before preoperative radio(chemo)therapy). Of note in the ypStage III subgroup, where the largest absolute benefit might be expected, no hint of survival improvement with chemotherapy was demonstrated.[27]

Patients with a tumour 10–15 cm from the anal verge was the only subgroup in which improved DFS was suggested after postoperative chemotherapy.[27] This finding is consistent with a Swedish retrospective population-based study.[5] The Swedish study included 436 patients with stage III disease who were younger than 75 years. Most patients received short-course preoperative radiotherapy, and postoperative chemotherapy was given to 42% of patients. The investigators noted a significant OS benefit from chemotherapy in patients with high rectal cancer, a trend towards benefit for mid rectal cancers, and no benefit for low rectal cancers.

The results of the trials comparing FU–OXA with FU-only postoperative chemotherapy are inconsistent. It remains intriguing why the large PETACC-6 study did not confirm the positive findings from the CAO/ARO/AIO-04 and the ADORE studies. In the CAO/ARO/AIO-04 trial, the FU schedule differed between arms during both the preoperative radiochemotherapy and the postoperative chemotherapy (Table 1). This study demonstrated higher local effectiveness (more pCRs) of the FU–OXA preoperative radiochemotherapy compared with FU-only radiochemotherapy.[20] For this reason, it is impossible to evaluate separately whether the survival benefit resulted from improved local effectiveness achieved by better preoperative radiochemotherapy or from eradication of distant disease by the postoperative chemotherapy. In addition, postoperative chemotherapy in the FU-only group comprised bolus FU without leucovorin, which is considered suboptimal, whereas leucovorin was given and FU was delivered as a continuous infusion in the FU–OXA group. These sources of bias do not exist in the PETACC-6 trial, in which the FU part of chemotherapy was identical in the two groups and the pCR rates after preoperative radiochemotherapy did not differ.[18] The negative results of the PETACC-6 trial are consistent with the negative results of the small CHRONICLE study, which compared FU–OXA with observation (HR 1.18, 95% CI: 0.43–3.26) (Table 1). Three of the trials reported only DFS without OS results because of a short follow-up. Although 3-year DFS is a surrogate endpoint for 5-year OS in the trials that evaluated the effectiveness of postoperative chemotherapy in colon cancer, it is unknown whether this also applies to rectal cancer. At present, the current meta-analysis does not allow the conclusion that FU–OXA provides survival benefits compared with FU-only or compared with observation. Full publications with longer follow-up are needed. The sources of inconsistency between the trial results could then be analysed. A recently published Cochrane meta-analysis included 21 randomized trials of rectal cancer that compared FU-only adjuvant chemotherapy with a control group (no adjuvant chemotherapy) in over 9000 patients.[38] Only one trial from that meta-analysis (the EORTC 22921 study) used preoperative radiotherapy; in three other trials, postoperative radiotherapy was given to all or most of the patients. Thus, most of the patients were treated with surgery alone. The Cochrane meta-analysis reported a 17% relative reduction in the risk of death among patients undergoing postoperative chemotherapy as compared with those undergoing observation (HR 0.83, 95% CI: 0.76–0.91, $P < 0.001$) and a 25% reduction in the risk of disease recurrence (HR 0.75, 95% CI: 0.68–0.83, $P < 0.001$). There is no good answer to the question why an effect of postoperative chemotherapy was found in patients treated with surgery alone (Cochrane meta-analysis) and not in patients given preoperative radio(chemo)therapy (the current meta-analysis and in the Bregoum et al. analysis).[27] The adherence to postoperative chemotherapy is lower in patients with rectal cancer having received radiochemotherapy (Tables 1 and 2) compared with patients with rectal cancer receiving surgery alone[39] or with those with colon cancer.[40,41] The most reliable cross-trial comparison was provided by two German parallel studies in which the same group of investigators randomized patients with colon or rectal cancer.[29] Three schedules of postoperative FU chemotherapy were compared. Randomization was performed after surgery in both locations. All patients with rectal cancer received radiochemotherapy 6–8 weeks after surgery. Six months of adjuvant treatment was given to 84% of patients with colon cancer and to 68% of those with rectal cancer ($P = 0.004$). This difference may at least partly be explained by the postradiation damage to pelvic bone marrow and bowel, which may increase chemotherapy-induced haematological and intestinal toxicity, but could also be attributed to the different surgery.

Does the benefit outweigh the harm?

As mentioned in the introduction section, there is huge variability in the recommendations for postoperative chemotherapy in patients with rectal cancer who have already received preoperative radio(chemo)therapy.[3] The recently published evidence, namely the Breugom et al.[27] and the current meta-analyses and the individual trials the Italian trial,[15] the PROCTOR/SCRIPT trial[16] and the CHRONICLE trial[17] support guidelines that do not recommend postoperative chemotherapy. On the other hand, it is possible that a small survival benefit of postoperative chemotherapy is present because sample sizes in the trials have been too small to detect differences in 5-year survival rates of less than 3–5% (type II error). Moreover, the meta-analyses might underestimate the chemotherapy effects

because of suboptimal methodology of some trials (e.g. randomization before the preoperative radio(chemo)therapy). Thus the question of whether the benefit outweighs the harm is justified.

Adverse effects of postoperative chemotherapy

A prospective study of colorectal cancer patients showed significant deterioration in the quality of life over the whole period of adjuvant chemotherapy compared with baseline values.[42] FU-only adjuvant chemotherapy may cause diarrhoea, nausea, vomiting, fatigue, pain related to stomatitis, abdominal cramps, worsening of cognitive function and loss of appetite.[42] In rare circumstances, complications may be life threatening and may require hospitalization. The mortality rates associated with postoperative chemotherapy are around 1% and seem to be higher among elderly patients.[43] Grade acute III+ toxicity was observed in 36%–40% of the patients given FU–OXA.[17,22] Diverting stoma reversal is usually postponed until completion of adjuvant chemotherapy. Thus, the life difficulties caused by the stoma last 4–6 months longer when adjuvant chemotherapy is given. Of note, delivery of postoperative chemotherapy increases the direct and indirect health care costs.

Postoperative chemotherapy in the treatment of rectal cancer also causes late adverse effects. Tiv et al.[44] and Mercier et al.[45] evaluated quality of life after a median follow-up of 4.6 years in patients treated in the EORTC 22921 randomized trial. The postoperative chemotherapy group reported significantly more pain, diarrhoea complaints, and lower physical and role functioning compared with the observation group. In a population-based study of colorectal cancer survivors 2–11 years after diagnosis, Mols et al.[46] reported that patients who received OXA more often reported neuropathy. Those with many neuropathy symptoms reported worse quality of life scores ($P < 0.01$).

Shared decision making

The significant controversy in the recommendations regarding the use of postoperative chemotherapy[3] and the new data imply that shared decision-making should take place, i.e., before an individual decision is made, patients must be informed about the uncertainties of the presence of a small treatment effect, the toxicity and about the lack of consensus between experts.[6] Judgement about whether the benefit outweighs the harm is subjective and should be left to the patient's discretion. For many patients, a small (putative) survival benefit does not merit FU-based chemotherapy.[47]

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Conflict of interest statement

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