# Biomarkers in colorectal cancer

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# PART I

## Adjuvant chemotherapy in rectal cancer treatment

# Chapter 2

## Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data

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# ABSTRACT




## BACKGROUND

The role of adjuvant chemotherapy for patients with rectal cancer after preoperative (chemo)radiotherapy and surgery is uncertain. We performed an individual patient data meta-analysis to compare adjuvant chemotherapy with observation in patients with rectal cancer.

## METHODS

We searched PubMed, MEDLINE, Embase, Web of Science, The Cochrane Library, CENTRAL, and conference abstracts to identify published and unpublished European randomised, controlled, phase III trials comparing observation with adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with non-metastatic rectal cancer. Primary end-point was overall survival. Secondary end-points were disease-free survival and distant recurrence rate.

The hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival, disease-free survival, and cumulative incidence of distant recurrences were calculated with Cox proportional hazards model. The regression models included strata defined by a term representing the distinct trials.

## FINDINGS

We included 1196 patients for analyses. For sensitivity analysis (all patients from eligible trials), 2195 patients were included. No significant differences in overall survival were found (HR 0·97, 95% CI 0·81-1·17, p=0·775) between the observation and chemotherapy arm. There were also no significant differences in overall survival for subgroups. Sensitivity analysis showed a HR of 0·95 (95% CI 0·82-1·09, p=0·430) for overall survival. Overall, no benefit of adjuvant chemotherapy was demonstrated for disease-free survival (HR 0·91, 95% CI 0·77-1·07, p=0·230) and distant recurrences (HR 0·94, 95% CI 0·78-1·14, p=0·523).

In subgroup analysis, patients with a tumour between 10 cm and 15 cm from the anal verge who received adjuvant chemotherapy had an improved disease-free survival (HR 0·59, 95% CI 0·40-0·85, p=0·005, $p_{interaction}$=0·107) and distant recurrence rate (HR 0·61, 95% CI 0·40-0·94, p=0·025, $p_{interaction}$=0·126).

## INTERPRETATION

Overall, 5-FU based adjuvant chemotherapy did not improve overall survival, disease-free survival and distant recurrence rate. However, our findings suggest that patients with a tumour located between 10 cm and 15 cm from the anal verge may benefit

from adjuvant chemotherapy in terms of disease-free survival and distant recurrences. Further research with regard to preoperative and postoperative treatment for this subgroup of patients is warranted.



## INTRODUCTION

Important advances have been made in rectal cancer treatment with the introduction of total mesorectal excision (TME), the addition of preoperative (chemo)radiotherapy to TME, and the ability of more accurate staging with magnetic resonance imaging (MRI).[1-9] Although locoregional recurrence rates and survival improved over the past years, distant recurrence rates did not. Unfortunately, still about 30% of all patients treated with curative intent will eventually develop distant metastases.[3, 6, 9] Adjuvant chemotherapy might decrease distant metastases by eliminating circulating tumour cells and micrometastases. However, the use of adjuvant chemotherapy in rectal cancer patients treated with preoperative (chemo)radiotherapy and surgery is still under debate.[10] For patients treated without preoperative (chemo)radiotherapy and TME surgery which results in high locoregional recurrence rates, adjuvant chemotherapy showed to be effective. This is demonstrated in a Cochrane review by Petersen et al. showing a risk reduction of 17% (HR 0·83, 95% CI 0·76-0·91) on overall survival and 25% (HR 0·75, 95% CI 0·68-0·83) on disease-free survival for patients who received adjuvant chemotherapy.[11] In this Cochrane review, only two studies administered preoperative (chemo)radiotherapy[12, 13] Of these, the EORTC 22921 study[12] did not demonstrate a benefit of adjuvant chemotherapy, while the QUASAR[13] did show a borderline significant improvement in overall survival for patients with rectal cancer. However, in the QUASAR study, only 21% of patients with rectal cancer or both colon and rectal cancer received preoperative radiotherapy.[13] Furthermore, a Japanese trial also demonstrated an improved overall and disease-free survival for stage III rectal cancer patients who were randomised to adjuvant chemotherapy after standardised mesorectal excision.[14] However, none of the patients received preoperative (chemo)radiotherapy and standardised mesorectal excision included selective lateral lymphadenectomy.[14]

In contrast, more recent trials comparing adjuvant chemotherapy and observation after preoperative (chemo)radiotherapy and TME surgery all did not demonstrate a benefit of adjuvant chemotherapy.[7, 15-17] With this individual patient data meta-analysis, we aim to investigate the effect of adjuvant 5-fluorouracil/leucovorin (5-FU/LV) based chemotherapy compared with observation after preoperative (chemo)radiotherapy and surgery for rectal cancer patients.

# METHODS



## SEARCH STRATEGY AND SELECTION CRITERIA

In cooperation with a trained librarian, we performed a search to identify published and unpublished European randomised, controlled, phase III trials comparing observation with adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with non-metastatic rectal cancer. Patients aged 18 years and older were eligible for inclusion. All current available preoperative treatment regimens, as well as both total mesorectal excision (TME) and conventional surgery were accepted for inclusion. Randomised controlled trials on adjuvant chemotherapy without an observation arm were excluded.

We searched PubMed, MEDLINE (OVID version), Embase (OVID version), Web of Science, The Cochrane Library, and CENTRAL from the date of their inception until June 26th, 2014 for relevant articles. We also searched abstracts from the most important international meetings. The search strategy consisted of the "AND" combination of three main concepts: "rectal carcinoma", "adjuvant chemotherapy", and "preoperative treatment". All relevant keyword variations were used for these three main concepts. Searches were limited to reports published in English. Literature screening of the retrieved articles was assessed by title and abstract, and conducted by two independent reviewers (MS and AJB). Studies that appeared to meet the inclusion criteria were selected for full-text review. Disagreements between the two independent reviewers were resolved by discussion.

We contacted the principal investigators of all eligible trials and requested individual patient data for baseline characteristics, tumour characteristics, preoperative treatment, surgery, adjuvant treatment, and follow-up.

## OUTCOMES

The primary end-point was overall survival. Secondary end-points were disease-free survival, and distant recurrences. All time-to-event variables were calculated from date of surgery. Overall survival was defined as time to death from any cause, or to end of follow-up (censored). Disease-free survival was defined as time to any recurrence or death, whichever occurred first, or end of follow-up (censored). Time to distant recurrence was defined as time to distant recurrence or end of follow-up (censored). The absence or presence of distant recurrence was confirmed by histology, cytology, or imaging.

## STATISTICAL ANALYSIS

To improve comparability between patients in the eligible trials, we included patients

with (y)pTNM stage II or III, who had a R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located ≤15 cm from the anal verge for the analysis. A sensitivity analysis of the primary end-point was performed in all patients who were originally included in the eligible trials.

Data were analysed for all included patients, as well as for the following patient subgroups: (y)pTNM stage (II *vs* III), tumour location from anal verge (<5 cm *vs* 5-9·9 cm *vs* ≥10 cm), type of resection (LAR *vs* APR), nodal status ((y)pN0 *vs* (y)pN1 *vs* (y)pN2), and preoperative treatment (short-course radiotherapy *vs* long-course radiotherapy *vs* long-course chemoradiotherapy).

The hazard ratio (HR) and 95% confidence interval (CI) for overall survival, disease-free survival, and the cause-specific hazard of distant recurrence, were calculated with Cox proportional hazards regression. The regression models included strata defined by a term representing the distinct trials. The cumulative incidence of distant recurrences was calculated with death as competing risk.[18] Median follow-up was calculated according to the reverse Kaplan-Meier method.[19] We did an interaction test of treatment efficacy with every subgroup for all outcome measures. Furthermore, analysis of the primary end-point was performed by trial, with all patients who were originally included in the eligible trials. These HRs and CIs slightly differ from the original articles, because more recent follow-up information was used.

The $I^2$ statistic, that should be interpreted "as the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies", was calculated.[20] Furthermore, the Q statistic was calculated to assess if significant heterogeneity between the included trials existed.

The findings of our meta-analysis are presented in forest plots, with HRs and 95% CIs for all patients and for the above-mentioned subgroups of patients.

Statistical analyses were performed using IBM SPSS Statistics, version 20·0, and R, version 3·1·0. A p-value of 0·05 or less was considered as statistically significant.

## ROLE OF THE FUNDING SOURCE

The funding sources had no role in the study design, management, data analysis, and data interpretation. AJB, MS, HP, and CJHvdV had access to all study data. The corresponding author had the final responsibility for the decision to submit for publication.

# RESULTS

Our initial search identified 1131 citations. We excluded 1035 citations by title because they did not meet eligibility criteria. We read the abstracts of the remaining 96 articles. Of these, three full-text randomised controlled trials were read.[7, 13, 16] Furthermore, we found one eligible trial that was presented during the 29th European Society for Radiotherapy and Oncology (ESTRO) congress in 2010[21], and one abstract that was presented during the European Cancer Congress in 2013.[22] After contacting the principal investigators of these five studies, we obtained individual patient data of the I-CNR-RT trial, the Chronicle trial, the PROCTOR-SCRIPT trial (CJHvdV, corresponding author, is principal investigator), and the EORTC 22921 trial (Figure 1).[7, 15-17] Table 1 shows the main characteristics of these trials. The risk of bias of all included studies was judged as low. Although none of the studies was blinded, we think this has not influenced the outcome measurements.

**Table 1**. Study characteristics

| | PROCTOR/SCRIPT | EORTC 22921 | Chronicle | Italian study |
|---|---|---|---|---|
| **Neo-adjuvant treatment** | | | | |
| **Chemoradiotherapy** | 25x1.8-2 Gy + 5-FU based chemotherapy | 25x1.8Gy + 5-FU based chemotherapy | 45 Gy + 5-FU based chemotherapy | 25x1.8Gy + 5-FU based chemotherapy |
| **Radiotherapy** | 5x5Gy | 25x1.8Gy | | |
| **Adjuvant treatment** | Mayo regime: 6 courses of 5-FU (425mg/m$^2$) and Folinic Acid (20mg/m$^2$)<br>Nordic regime:12 courses of 5-FU (500mg/m$^2$) and Folinic Acid (60mg/m$^2$)<br>8 courses every three weeks of oral capecitabine (1250mg/m$^2$) twice daily for 14 days | 4 courses every three weeks of 5-FU (350mg/ m$^2$) and Folinic Acid (20mg/ m$^2$) | 6 courses every three weeks of oxaliplatin (130mg m$^2$) and oral capecitabine (1000mg/m$^2$) twice daily for 14 days (XELOX) | 6 courses of 5-FU (350mg/ m$^2$) and Folinic Acid (20mg/ m$^2$) |
| **Start of accrual** | March 2000 | April 1993 | November 2004 | September 1992 |
| **End of accrual** | January 2013 | March 2003 | April 2008 | January 2001 |
| **Disease stage** | (y)pTNM II, III | Clinical stage T3,T4 | (y)pTNM II,III | Clinical stage T3,T4 |
| **Resection margin** | R0,R1 | R0 | R0 | R0 |
| **TME resection performed** | Yes | Halfway of the inclusion | Yes | No |
| **Timing of randomisation** | After surgery | Before surgery | After surgery | Before surgery |
| **Number of patients eligible for analysis (original study)** | 437 | 1011 | 113 | 634 |
| **Number of patients eligible for analysis in this article** | 403 | 473 | 75 | 245 |

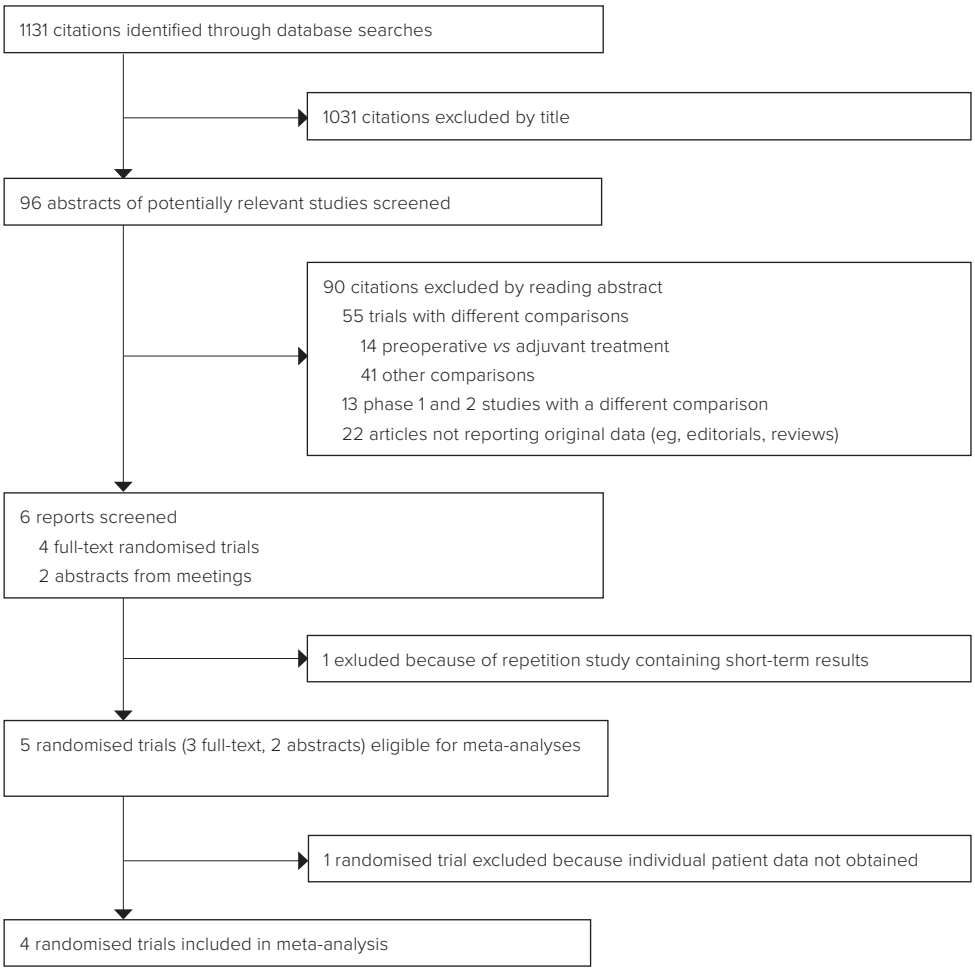


**Figure 1.** Selection of eligible trials

In total, there were 2195 patients included in four trials. To improve comparability, we selected 1196 patients for the analysis with (y)pTNM stage II or III, who had a R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located ≤15cm from the anal verge.

Of these 1196 patients, 598 patients had observation after surgery, and 598 patients received adjuvant chemotherapy. Patient characteristics are shown in Table 2. Median follow-up was 7·0 years (range: 0·0 - 17·4 years; two patients died on day of surgery).

**Table 2**. Patient characteristics

| Characteristics | Total (n = 1196) | Observation (n =598) | Chemotherapy (n =598) |
|---|---|---|---|
| **Trial** | | | |
| **Italian** | 245 (20.5) | 112 (18.7) | 133 (22.2) |
| **PROCTOR-SCRIPT** | 403 (33.7) | 204 (34.1) | 199 (33.3) |
| **Chronicle** | 75 (6.3) | 45 (7.5) | 30 (5.0) |
| **EORTC 22921** | 473 (39.5) | 237 (39.6) | 236 (39.5) |
| **Age (years)** | 61.50 ±9.60 | 62.00 ±9.63 | 61.00 ±9.57 |
| **Gender** | | | |
| **Male** | 810 (67.7) | 410 (68.6) | 400 (66.9) |
| **Female** | 386 (32.3) | 188 (31.4) | 198 (33.1) |
| **Preoperative treatment** | | | |
| **25 Gy** | 348 (29.1) | 179 (29.9) | 169 (28.3) |
| **45 Gy** | 267 (22.3) | 134 (22.4) | 133 (22.2) |
| **45 Gy + FU based chemo-therapy** | 581 (48.6) | 285 (47.7) | 296 (49.5) |
| **Type of resection** | | | |
| **LAR** | 726 (60.7) | 362 (60.5) | 364 (60.9) |
| **APR** | 470 (39.3) | 236 (39.5) | 234 (39.1) |
| **Tumour location from anal verge** | | | |
| **< 5 cm** | 381 (31.9) | 187 (31.3) | 194 (32.4) |
| **5 – 9.9 cm** | 519 (43.4) | 256 (42.8) | 263 (44.0) |
| **≥ 10 cm** | 281 (23.5) | 144 (24.1) | 137 (22.9) |
| **Unknown** | 15 (1.3) | 11 (1.8) | 4 (0.7) |
| **(y)pTNM** | | | |
| **II** | 459 (38.4) | 207 (34.6) | 252 (42.1) |
| **III** | 737 (61.6) | 391 (65.4) | 346 (57.9) |

Data are presented as median ± SD or as *n* (%)

## OVERALL SURVIVAL

A total of 451 patients died. Figure 2A shows a forest plot of hazard ratios for overall survival for all patients and for subgroups. Overall, no benefit in overall survival was observed for patients who received adjuvant chemotherapy compared with observation (HR 0·97, 95% CI 0·81-1·17, p=0·775). Also in subgroup analysis, no significant differences in overall survival were found. Sensitivity analysis of all 2195 patients showed a HR of 0·95 (95% CI 0·82-1·09, p=0·430). Supplementary Figure 1 shows a forest plot of hazard ratios for overall survival by study.

We found no heterogeneity in treatment effect between the four trials ($I^2$=0%, p=0·605).

## DISEASE-FREE SURVIVAL

In total, there were 580 events. The disease-free survival results are shown in Figure 2B. Overall, we observed no statistically significant difference in disease-free survival for

patients who received adjuvant chemotherapy compared with observation (HR 0·91, 95% CI 0·77-1·07, p=0·230). In subgroup analysis, patients with a tumour between 10 cm and 15 cm from the anal verge who received adjuvant chemotherapy had an improved disease-free survival (HR 0·59, 95% CI 0·40-0·85, p=0·005), without a significant interaction between distance from the anal verge (<5 cm *vs* 5-9·9 cm *vs* ≥10 cm) and randomisation arm (p=0·107). For the other subgroups, there were no differences in disease-free survival.

There was no heterogeneity of adjuvant chemotherapy effect among the four trials ($I^2$=0%, p=0·836).

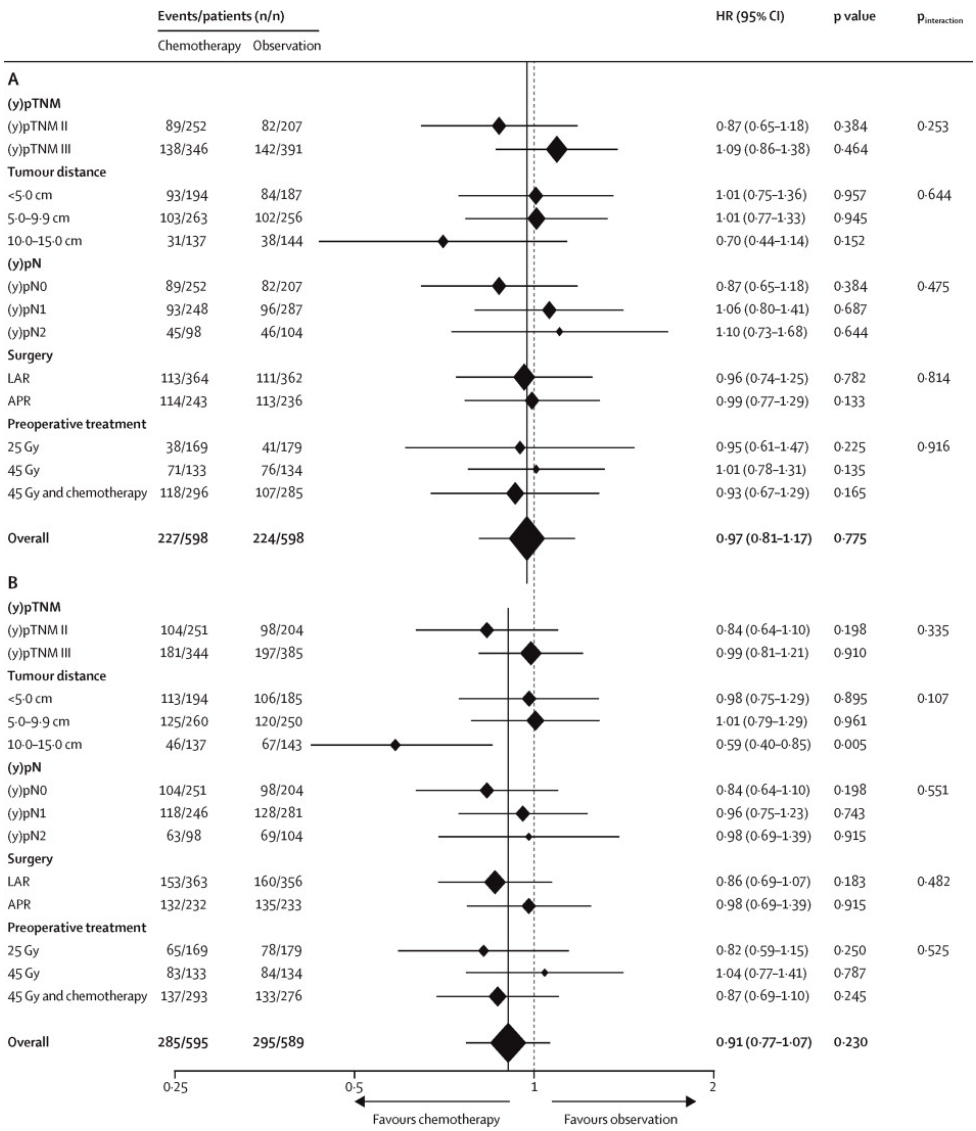


**Figure 2.** Overall survival (A) and disease-free survival (B) for all patients and by patient subgroups

Footnote Figure 2: The size of the diamonds represents the proportion of patients

## DISTANT RECURRENCE

There were 415 distant recurrences. Overall, we did not observe a significant benefit of adjuvant chemotherapy. At five years, the cumulative incidence for distant recurrences was 36·51% (95% CI 32·64%-40·84%) in the observation arm and 35·50% (95% CI 31·70%-39·76%) in the chemotherapy arm (HR 0·94, 95% CI 0·78-1·14, p=0·523; Figure 3; Figure 4). However, patients with a tumour between 10 cm and 15 cm from the anal verge showed a benefit of adjuvant chemotherapy with regard to distant recurrence (HR 0·61, 95% CI 0·40-0·94, p=0·025), without a significant interaction between distance from the anal verge and randomisation arm (p=0·126). Similar to disease-free survival, there were no significant differences for the other subgroups between observation and adjuvant chemotherapy (Figure 3).

We found no heterogeneity in treatment effect between the four trials ($I^2$=0%, p=0·617).

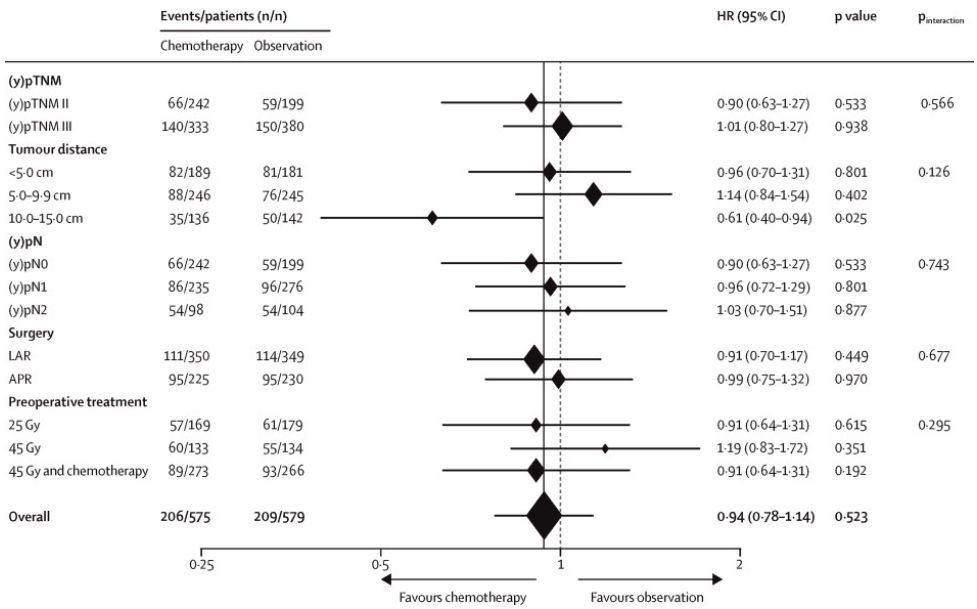


**Figure 3.** Distant recurrence

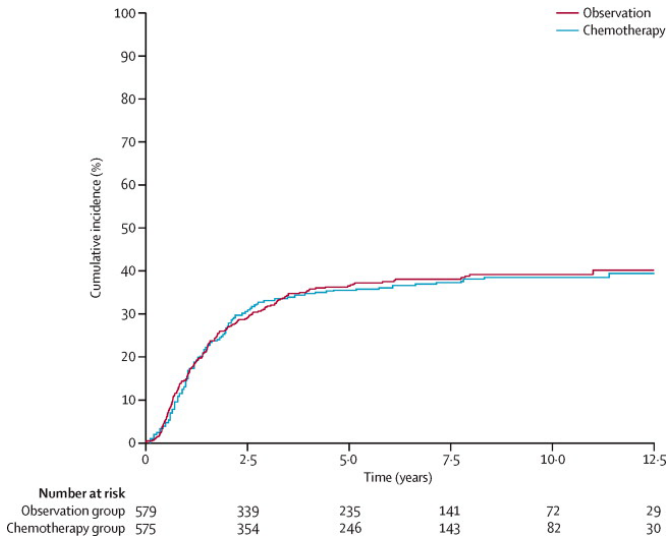


**Figure 4** Cumulative incidence of distant recurrences

# DISCUSSION

This meta-analysis pooled individual patient data of four randomised controlled trials comparing observation with adjuvant 5-FU based chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer. Overall, no benefit of 5-FU based adjuvant chemotherapy was shown with regard to overall survival, disease-free survival, and distant recurrences after a median follow-up of 7·0 years. However, our findings suggest that patients with a tumour located between 10 cm and 15 cm from the anal verge may benefit from adjuvant chemotherapy in terms of disease-free survival and distant recurrences.

Although a clear benefit of adjuvant chemotherapy has been demonstrated for patients with stage III colon cancer[23-26], this is not the case for patients with non-metastatic rectal cancer treated with preoperative (chemo)radiotherapy and surgery. The inconclusive evidence on the use of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer is reflected by international differences in guidelines varying from not recommending adjuvant chemotherapy to recommending adjuvant chemotherapy for stage II and III rectal cancer patients.[27-30] The latter is based on extrapolation from phase III trials for adjuvant treatment for colon cancer[23-26], as well as from trials in patients with rectal cancer who were treated without preoperative (chemo)radiotherapy.[11]

However, even though four out of five European randomised controlled trials comparing adjuvant chemotherapy with observation after receiving preoperative (chemo)radiotherapy and surgery did not demonstrate a clinical relevant or statistical significant benefit of adjuvant chemotherapy[7, 15-17], none has individually put an end to the discussion on the role of adjuvant chemotherapy. This could be partly explained by the fact that two of these trials did not have sufficient power.[15, 16] Only the QUASAR trial found a borderline significant improvement in overall survival for patients with rectal cancer who were randomised to adjuvant chemotherapy, but only 21% of patients with rectal cancer or both rectal and colon cancer had preoperative radiotherapy and no patient received chemoradiotherapy.[13]

By pooling the individual patient data from the I-CNR-RT trial, the EORTC 22921 trial, the Chronicle trial, and the PROCTOR-SCRIPT trial[7, 15-17], we think this meta-analysis is the most robust analysis of the role of adjuvant 5-FU based chemotherapy for patients with rectal cancer to date, enabling to increase the statistical power, to improve comparability between the patients in the four individual trials, and to perform subgroup analysis.

Besides the embryological, anatomical, and physiological differences between colon and rectum, accumulating evidence suggests that colon and rectal cancer differ in oncogenesis.[31] Differences include reduced microsatellite instability (MSI) and BRAF mutations in rectal cancer compared with colon cancer.[32-34] Furthermore, in the last decade, different gene expression profiles between colon and rectal tumours, as well as within the colon were observed.[35, 36] These differences between colon and rectal tumours might contribute to the differences in beneficial effect of adjuvant chemotherapy between colon and rectal cancer. In contrast, no clear differences in *KRAS* mutations between colon and rectal tumours were demonstrated.[37-40]

Interestingly, despite the suggestion that colon and rectal tumours differ in carcinogenesis, the definition of the rectum is not consistent across countries with regard to distance from the anal verge and location of the peritoneal reflection. Although the results of our meta-analysis overall do not demonstrate a benefit of adjuvant chemotherapy in overall survival, disease-free survival, and distant recurrences, our results suggest that patients with a tumour between 10 cm and 15 cm from the anal verge may benefit from adjuvant chemotherapy in terms of disease-free survival and distant recurrences. This raises the question whether tumours between 10 cm and 15 cm from the anal verge should be defined as colon tumours rather than rectal tumours, that may require other treatment approaches than rectal tumours below 10 cm from the anal verge. However, since there is no significant interaction between distance

from the anal verge and randomisation arm, these results are not definitive. Further investigation with regard to preoperative and postoperative treatment for patients with a tumour between 10 cm and 15 cm from the anal verge is warranted to draw definitive conclusions for these patients. In contrast, no benefit of adjuvant chemotherapy was demonstrated for other subgroups. Unfortunately, patients with ypTNM 0 and ypTNM I were only included in the I-CNR-RT trial, and partly in the EORTC 22921 trial. Therefore, it was not possible to perform a meta-analysis on ypTNM stage 0 and ypTNM stage I, although this would have been interesting.

An individual patient data meta-analysis has advantages over an aggregate data meta-analysis, as for example the possibility to obtain results for specific subgroups.[41] Although we think this individual patient data meta-analysis on the effect of adjuvant chemotherapy in rectal cancer patients after preoperative (chemo)radiotherapy and surgery provides the best current available evidence, this study has some limitations. A well-recognised problem in randomised controlled trials is to obtain sufficient power.[42] Patients´ and clinicians´ treatment preferences for either observation or adjuvant chemotherapy, contributed to the fact that two of the included trials in this meta-analysis had to close their study before the intended number of patients was reached.[15, 16] Another well-known problem of trials investigating the role of adjuvant chemotherapy in patients with rectal cancer after preoperative (chemo)radiotherapy and surgery is adjuvant chemotherapy compliance. In the PROCTOR-SCRIPT trial, adjuvant chemotherapy compliance was 73.6% (randomisation postoperatively).[15] In the EORTC 22921 trial (randomisation preoperatively) 43% completed all cycles of chemotherapy[7], while this amounted 48% in the Chronicle trial (randomisation postoperatively).[16] In the I-CNR-RT trial (randomisation preoperatively), 55% received three to six courses chemotherapy.[17] In theory, this could have influenced the results, although we think it is unlikely that this has influenced the overall outcomes significantly. For example, in the per-protocol analysis of the PROCTOR-SCRIPT trial[15], no benefit of adjuvant chemotherapy was demonstrated in patients who completed all cycles of adjuvant chemotherapy. Besides, the EORTC 22921 trial, the I-CNR-RT trial, and the PROCTOR-SCRIPT trial all had a long accrual period. For example, TME surgery was not yet standard of care during the greatest part of the inclusion period of the I-CNR-RT trial, and became standard of care halfway the inclusion period of the EORTC 22921 trial. Lastly, the QUASAR trial is not included in our meta-analysis, because we unfortunately did not obtain the individual patient data.

If patients with a tumour between 10 cm and 15 cm from the anal verge indeed do benefit from adjuvant chemotherapy, the question is whether fluoropyrimidine monotherapy or combination chemotherapy should be administered. No clear evidence of superiority

of fluoropyrimidine monotherapy or combination chemotherapy existed at the start of most of the included trials. Three out of four trials included in this meta-analysis used fluoropyrimidine monotherapy.[7, 15-17] In 2009, the MOSAIC trial demonstrated an improved disease-free survival and overall survival for patients with colon cancer by adding oxaliplatin to 5-FU/LV.[26, 43] For this reason, the Chronicle trial administered combination chemotherapy.[16] Recently, the ADORE trial showed that there seems to be a benefit of adjuvant FOLFOX over 5-FU/LV for patients with ypTNM stage II or III rectal cancer.[44] Besides, the results of the CAO/ARO/AIO-04 trial (presented during the 2014 ASCO Annual Meeting) demonstrated a benefit of adjuvant combination chemotherapy over 5-FU monotherapy.[45] Because the lack of an observation arm in both studies, these studies were unfortunately not eligible in this meta-analysis. The question whether there is a benefit of adjuvant combination chemotherapy over observation remains unanswered.

In conclusion, overall, 5-FU based adjuvant chemotherapy did not improve overall survival, disease-free survival and distant recurrences compared with observation in rectal cancer patients. However, our findings suggest that patients with a tumour located between 10 cm and 15 cm from the anal verge may benefit from adjuvant chemotherapy in terms of disease-free survival and distant recurrences. Further research with regard to preoperative and postoperative treatment for this subgroup of patients is warranted.

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