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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Summary

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

Methods We searched PubMed, Medline, Embase, Web of Science, the Cochrane Library, CENTRAL, and conference abstracts to identify European randomised, controlled, phase 3 trials comparing observation with adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with non-metastatic rectal cancer. The primary endpoint of interest was overall survival.

Findings We analysed data from four eligible trials, including data from 1196 patients with (y)pTNM stage II or III disease, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm of the anal verge. We found no significant differences in overall survival between patients who received adjuvant chemotherapy and those who underwent observation (hazard ratio [HR] 0·97, 95% CI 0·81–1·17; p=0·775); there were no significant differences in overall survival in subgroup analyses. Overall, adjuvant chemotherapy did not significantly improve disease-free survival (HR 0·91, 95% CI 0·77–1·07; p=0·230) or distant recurrences (0·94, 0·78–1·14; p=0·523) compared with observation. However, in subgroup analyses, patients with a tumour 10–15 cm from the anal verge had improved disease-free survival (0·59, 0·40–0·85; p=0·005, $p_{interaction}$=0·107) and fewer distant recurrences (0·61, 0·40–0·94; p=0·025, $p_{interaction}$=0·126) when treated with adjuvant chemotherapy compared with patients undergoing observation.

Interpretation Overall, adjuvant fluorouracil-based chemotherapy did not improve overall survival, disease-free survival, or distant recurrences. However, adjuvant chemotherapy might benefit patients with a tumour 10–15 cm from the anal verge in terms of disease-free survival and distant recurrence. Further studies of preoperative and postoperative treatment for this subgroup of patients are warranted.

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Introduction

Important advances have been made in the treatment of rectal cancer with the introduction of total mesorectal excision, the addition of preoperative (chemo)radiotherapy to total mesorectal excision, and the ability to more accurately stage rectal cancer with MRI.[1–9] Although locoregional recurrence and survival have improved, distant recurrence has not. About 30% of all patients treated with curative intent will eventually develop distant metastases.[3,6,9] Adjuvant chemotherapy might prevent distant metastases by eliminating circulating tumour cells and micrometastases. However, the use of adjuvant chemotherapy for patients with rectal cancer treated with preoperative (chemo)radiotherapy and surgery is debated.[10] For patients treated without preoperative (chemo)radiotherapy and total mesorectal excision surgery, which results in high numbers of locoregional recurrences, adjuvant chemotherapy is effective. In a systematic review and meta-analysis, Petersen and colleagues[11] showed that adjuvant chemotherapy improved overall survival (HR 0·83, 95% CI 0·76–0·91) and disease-free survival (HR 0·75, 0·68–0·83).[11] However, their review included only two studies[12,13] in which patients had had preoperative (chemo)radiotherapy. The investigators of the EORTC 22921 study[12] did not report a benefit of adjuvant chemotherapy, while those of QUASAR[13] showed 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, results of a Japanese trial also showed improved overall survival and disease-free survival in patients with stage III rectal cancer who were randomly assigned 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]

By contrast, results of other trials comparing adjuvant chemotherapy and observation after preoperative (chemo)radiotherapy and total mesorectal excision surgery did not show a benefit of adjuvant chemotherapy.[7,15–17]

We did a meta-analysis of individual patient data to investigate the effect of adjuvant fluorouracil and folinic acid chemotherapy compared with observation after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer.

Methods

Search strategy and selection criteria

In cooperation with a trained librarian, we searched for published and unpublished European randomised, controlled, phase 3 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 available preoperative treatment regimens, as well as both total mesorectal excision and conventional surgery, were accepted for inclusion. We excluded randomised controlled trials of adjuvant chemotherapy without an observation group.

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 26, 2014, for relevant articles. We also searched abstracts from the most important international meetings: ECCO, ESTRO, ESSO, and ESMO. We searched for "rectal carcinoma" AND "adjuvant chemotherapy" AND "preoperative treatment". All relevant keyword variations were used for these three terms. We restricted our searches to reports published in English. Two independent reviewers (MS and AJB) screened the title and abstract of retrieved articles. Studies that seemed to meet the inclusion criteria were selected for full-text review. Disagreements between the two 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 endpoint of interest was overall survival. Secondary endpoints 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 histological assessment, cytological assessment, or imaging.

Statistical analysis

To improve comparability between patients in the eligible trials, we included patients with (post-neoadjuvant) pathological TNM—ie, (y)pTNM—stage II or III disease, who had a R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located no more than 15 cm from the anal verge. We did a sensitivity analysis of the primary endpoint for all patients who were originally included in the eligible trials.

We analysed data for all included patients, as well as for the following subgroups: (y)pTNM stage (II *vs* III), tumour location from anal verge (<5·0 cm *vs* 5·0–9·9 cm *vs* ≥10 cm), type of resection (low anterior resection *vs* abdominoperineal resection), nodal status ([y]pN0 *vs* [y]pN1 *vs* [y]pN2), and preoperative treatment (short-course radiotherapy *vs* long-course radiotherapy *vs* long-course chemoradiotherapy).

We calculated hazard ratios and 95% CIs for overall survival, disease-free survival, and the cause-specific risk

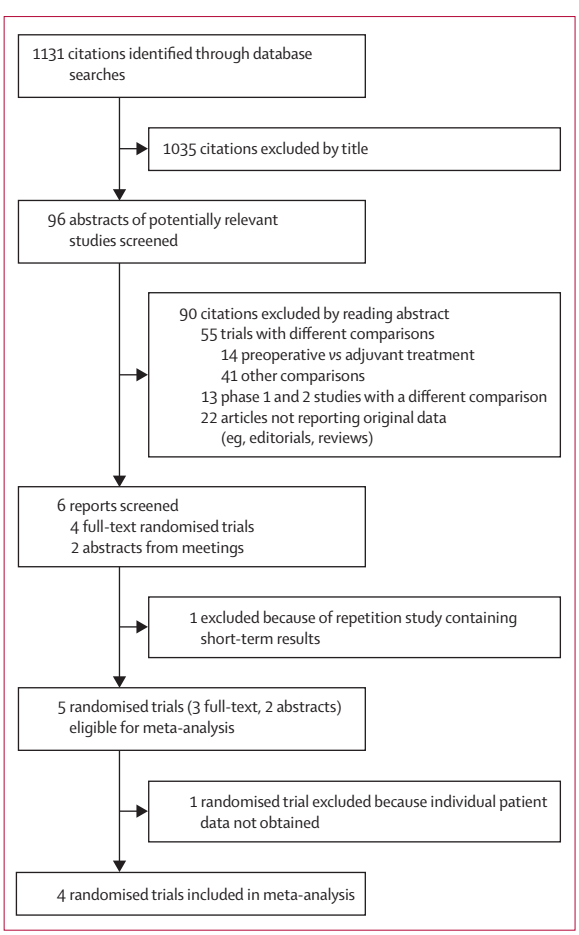

Figure 1: **Study selection**

	I-CNR-RT[17]	PROCTOR-SCRIPT[15]	EORTC 22921[7]	CHRONICLE[16]
Preoperative treatment				
Chemoradiotherapy	25 doses of 1·8 Gy and fluorouracil-based chemotherapy	25 doses of 1·8–2·0 Gy and fluorouracil-based chemotherapy	25 doses of 1·8 Gy and fluorouracil-based chemotherapy	45 Gy and fluorouracil-based chemotherapy
Radiotherapy	..	Five doses of 5 Gy or 25 doses of 1·8–2·0 Gy	25 doses of 1·8 Gy	..
Adjuvant treatment	Six courses of fluorouracil (350 mg/m²) and folinic acid (20 mg/m²)	Mayo regimen: six courses of fluorouracil (425 mg/m²) and folinic acid (20 mg/m²) Nordic regimen: 12 courses of fluorouracil (500 mg/m²) and folinic acid (60 mg/m²); eight courses every 3 weeks of oral capecitabine (1250 mg/m²) twice daily for 14 days	Four courses every 3 weeks of fluorouracil (350 mg/m²) and folinic acid (20 mg/m²)	Six courses every 3 weeks of oxaliplatin (130 mg/m²) and oral capecitabine (1000 mg/m²) twice daily for 14 days
Start of accrual	September, 1992	March, 2000	April, 1993	November, 2004
End of accrual	January, 2001	January, 2013	March, 2003	April, 2008
Disease stage	Clinical stage T3, T4*	(y)pTNM II, III	Clinical stage T3, T4*	(y)pTNM II, III
Resection margin	R0	R0, R1	R0	R0
Total mesorectal excision done?	No	Yes	Halfway inclusion	Yes
Timing of randomisation	Before surgery	After surgery	Before surgery	After surgery
Number of patients eligible for analysis in original report	634	437	1011	113
Number of patients eligible for analysis for this meta-analysis	245	403	473	75

*We included patients based on (post-neoadjuvant) pathological TNM stage—ie, (y)pTNM stage.

Table 1: **Study characteristics**

	Observation (n=598)	Chemotherapy (n=598)
Trial		
I-CNR-RT[17]	112 (19%)	133 (22%)
PROCTOR-SCRIPT[15]	204 (34%)	199 (33%)
CHRONICLE[16]	45 (8%)	30 (5%)
EORTC 22921[7]	237 (40%)	236 (39%)
Age (years)	62 (54–68)	61 (55–68)
Sex		
Men	410 (69%)	400 (67%)
Women	188 (31%)	198 (33%)
Preoperative treatment		
25 Gy	179 (30%)	169 (28%)
45 Gy	134 (22%)	133 (22%)
45 Gy and fluorouracil-based chemotherapy	285 (48%)	296 (49%)
Type of resection		
Lower anterior resection	362 (61%)	364 (61%)
Abdominoperineal resection	236 (39%)	234 (39%)
Tumour distance from anal verge		
<5·0 cm	187 (31%)	194 (32%)
5·0–9·9 cm	256 (43%)	263 (44%)
≥10·0 cm	144 (24%)	137 (23%)
Unknown	11 (2%)	4 (<1%%)
(y)pTNM		
II	207 (35%)	252 (42%)
III	391 (65%)	346 (58%)

Data are n (%) or median (IQR). (y)pTNM=(post-neoadjuvant) pathological TNM stage.

Table 2: **Patient characteristics**

of distant recurrence, with Cox proportional hazards regression. The regression models included strata defined by a term representing the distinct trials. We calculated the cumulative incidence of distant recurrence with death as competing risk.[18] We calculated median follow-up according to the reverse Kaplan-Meier method.[19] We did an interaction test of treatment efficacy for each subgroup for all outcome measures. We also analysed the primary endpoint by trial, with all patients who were originally included in the eligible trials. These HRs and CIs slightly differ from the original articles because we used more recent follow-up information.

We calculated I^2 and Q to assess whether significant heterogeneity existed between the included trials.[20] We did statistical analyses with SPSS (version 20.0) and R (version 3.1.0). We considered a p value of 0·05 or less as statistically significant.

Role of the funding source

This study had no funding. The funders of the original studies 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 (figure 1).[7,13,16] We also found one eligible trial[21] that

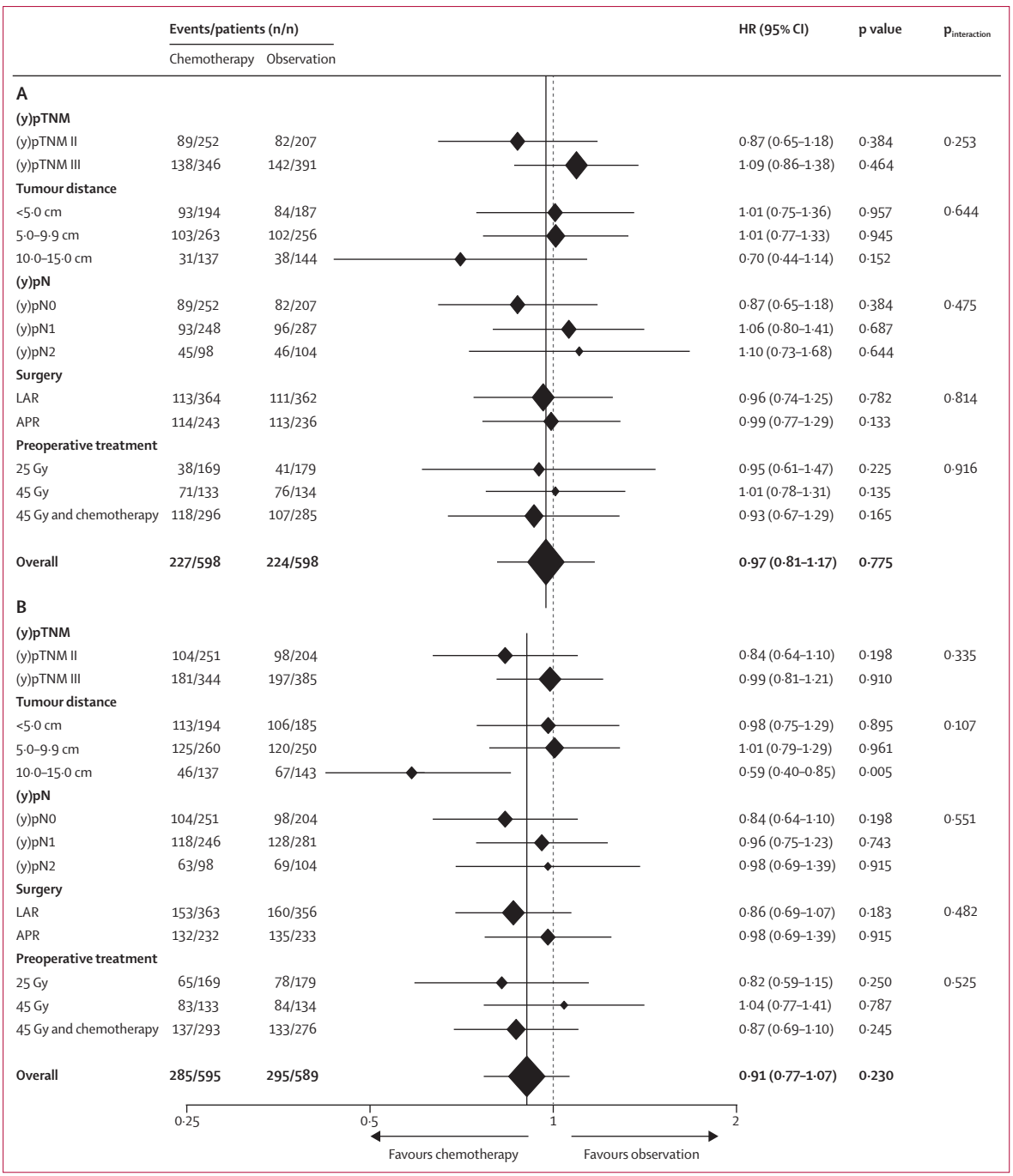

Figure 2: **Overall survival (A) and disease-free survival (B) for all patients and by patient subgroups**
The size of the diamonds represents the proportion of patients. LAR=lower anterior resection. APR=abdominoperineal resection.

was presented during the European Society for Radiotherapy and Oncology congress in 2010, and one abstract[22] that was presented during the European Cancer Congress in 2013. These abstracts were later published in full.[15,17] We were able to obtain individual patient data for the I-CNR-RT trial,[17] the CHRONICLE trial,[16] the PROCTOR-SCRIPT trial,[15] and the EORTC 22921 trial.[7] Table 1 shows the main characteristics of these trials. The risk of bias of all included studies was judged to be low.

2195 patients were included in the four trials. 1196 patients with (y)pTNM stage II or III disease, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm of the anal verge were included in our

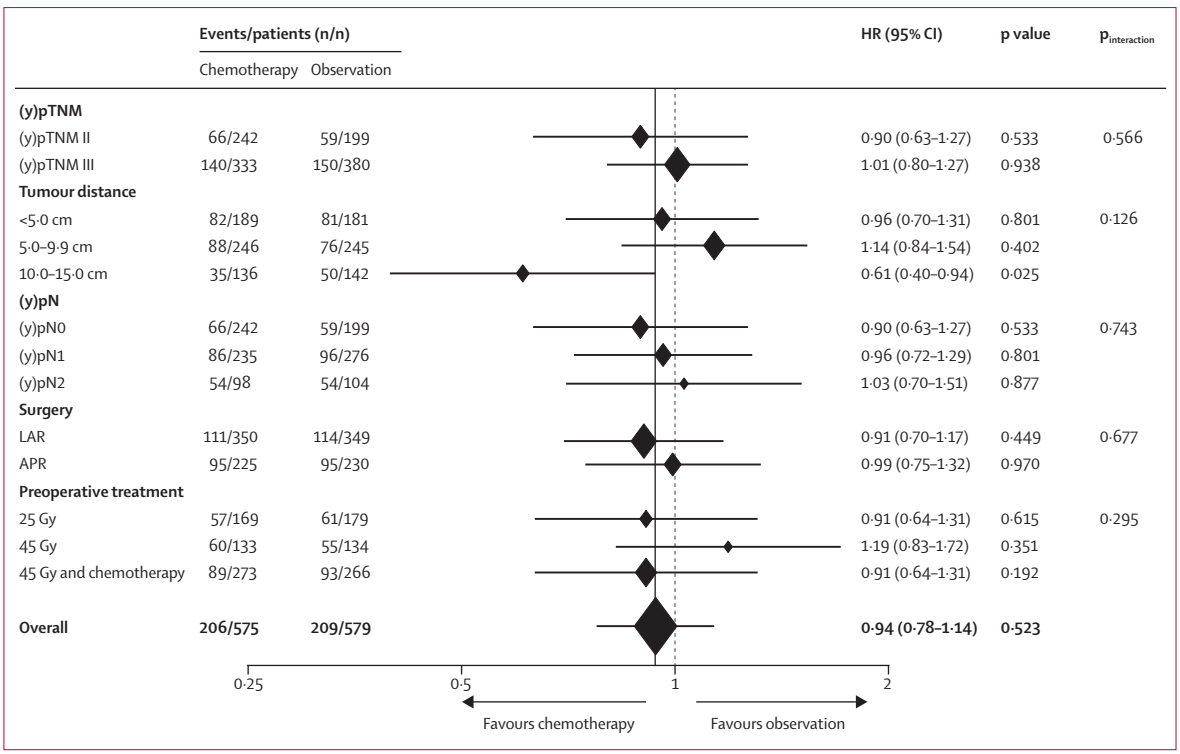

Figure 3: **Distant recurrence**
The size of the diamonds represents the proportion of patients. LAR=lower anterior resection. APR=abdominoperineal resection.

analyses. Of these 1196 patients, 598 had observation after surgery, and 598 received adjuvant chemotherapy. Table 2 shows patient characteristics. Median follow-up was 7·0 years (IQR 4·3–10·2; two patients died on day of surgery).

451 patients died. Overall, adjuvant chemotherapy provided no significant benefit in overall survival compared with observation (HR 0·97, 95% CI 0·81–1·17; p=0·775; figure 2A). In subgroup analyses, we recorded no significant differences in overall survival between the groups. Sensitivity analysis of all 2195 patients showed a HR of 0·95 (95% CI 0·82–1·09, p=0·430). A forest plot of hazard ratios for overall survival by study can be found in the appendix. We found no heterogeneity in treatment effect on overall survival between the four trials (I^2=0%, p=0·605).

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580 events disease-free survival events occurred. For all included patients, we detected no significant difference in disease-free survival between patients who received adjuvant chemotherapy and those who underwent observation (HR 0·91, 95% CI 0·77–1·07, p=0·230; figure 2B). In subgroup analysis, patients with a tumour 10–15 cm from the anal verge who received adjuvant chemotherapy had improved disease-free survival (HR 0·59, 95% CI 0·40–0·85, p=0·005), with no significant interaction between distance from the anal verge (<5·0 cm *vs* 5·0–9·9 cm *vs* ≥10·0 cm) and treatment group (figure 2B). For the other subgroups, we recorded no significant differences in disease-free survival. The effect of adjuvant chemotherapy on disease-free survival was not heterogeneous among the four trials (I^2=0%, p=0·836).

We recorded 415 distant recurrences. Overall, we detected no significant benefit of adjuvant chemotherapy compared with observation (figure 3). At 5 years, the cumulative incidence for distant recurrences was 36·5% (95% CI 32·6–40·8) in the observation group and 35·5% (31·7–39·8) in the chemotherapy group (HR 0·94, 95% CI 0·78–1·14, p=0·523; figures 3 and 4). However, patients with a tumour 10–15 cm from the anal verge had a benefit with adjuvant chemotherapy compared with observation in terms of distant recurrence (HR 0·61, 0·40–0·94; p=0·025), without a significant interaction between distance from the anal verge and treatment group (figure 3). We detected no significant differences for the other subgroups between observation and adjuvant chemotherapy (figure 3). We found no heterogeneity in treatment effect on distant recurrence between the four trials (I^2=0%, p=0·617).

Discussion

Our findings show that fluorouracil-based adjuvant chemotherapy has no benefit on overall survival, disease-free survival, and distant recurrences after a median follow-up of 7·0 years in patients with (y)pTNM stage II or III rectal cancer, who had an R0 resection, had a low

anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm of the anal verge. However, our findings suggest that adjuvant chemotherapy might improve disease-free survival and distant recurrences in patients with a tumour located 10–15 cm from the anal verge.

Although a clear benefit of adjuvant chemotherapy has been shown 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 shown by international differences in treatment guidelines.[27–30] Advice to give adjuvant chemotherapy to patients with stage II or III rectal cancer is based on extrapolation of results from phase 3 trials of 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]

Despite four of five European randomised controlled trials comparing adjuvant chemotherapy with observation after preoperative (chemo)radiotherapy and surgery showing no benefit of adjuvant chemotherapy,[7, 15–17] none have individually ended the discussion about the role of adjuvant chemotherapy. This might partly be because two of these trials[15,16] did not have sufficient power. The QUASAR trial[13] showed a borderline significant improvement in overall survival for patients with rectal cancer who were assigned 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. By pooling individual patient data, we think that this meta-analysis is the most robust analysis to date of the role of adjuvant fluorouracil-based chemotherapy for patients with rectal cancer; combining the individual patient data increased the statistical power, and enabled us to improve comparability between patients in the four individual trials, as well as to do subgroup analyses. Although none of the studies were masked, we do not think that this affected the outcome measurements.

Aside from embryological, anatomical, and physiological differences between the colon and rectum, colon and rectal cancer seem to differ in oncogenesis.[31] Rectal cancer has less microsatellite instability and fewer *BRAF* mutations than does colon cancer.[32–34] Furthermore, different gene expression profiles between colon and rectal tumours have been reported.[35,36] These differences might contribute to different effects of adjuvant chemotherapy in colon and rectal cancer. By contrast, no clear differences have been detected in *KRAS* mutations between colon and rectal tumours.[37–40]

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. The findings from our subgroup analysis raise the question of whether tumours between 10 cm and 15 cm from the anal verge should be defined as colon tumours rather than rectal tumours, which might require different treatments to rectal tumours less than 10 cm from the anal verge. However, because we detected no significant interaction between distance from the anal verge and treatment group, these results are not definitive. Further investigation of preoperative and postoperative treatment for patients with a tumour 10–15 cm from the anal verge is warranted to draw definitive conclusions for these patients. We showed no benefit of adjuvant chemotherapy for other subgroups. Patients with ypTNM 0 and ypTNM I cancer were only included in the I-CNR-RT trial, and partly in the EORTC 22921 trial. Therefore, we could not do a meta-analysis of patients with ypTNM stage 0 and ypTNM stage I disease.

A meta-analysis of individual patient data has advantages over a meta-analysis of aggregate data, such as the possibility to obtain results for subgroups.[41] Although we think that our study provides the best available evidence, it has some limitations. A well-known challenge in randomised controlled trials is to obtain sufficient power.[42] Patients' and clinicians' treatment preferences contributed to the fact that two trials[15,16] in this meta-analysis had to stop before the intended number of patients were recruited. Compliance to adjuvant chemotherapy is recognised as a problem of studies investigating the role of adjuvant chemotherapy in patients with rectal cancer after preoperative (chemo)radiotherapy and surgery. In the PROCTOR-SCRIPT trial (patients postoperatively

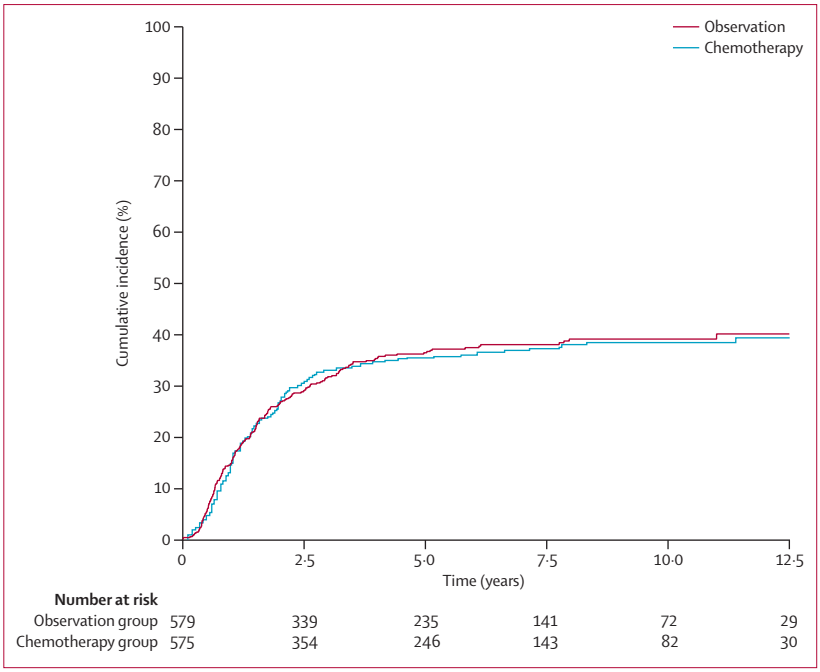

Figure 4: **Cumulative incidence of distant recurrences**

randomly assigned), 73·6% of patients complied with treatment.[15] In the EORTC 22921 trial (patients preoperatively randomly assigned), 43% completed all cycles of chemotherapy,[7] compared with 48% in the CHRONICLE trial (patients postoperatively randomly assigned).[16] In the I-CNR-RT trial (patients preoperatively randomly assigned), 55% of participants received three to six courses of chemotherapy.[17] In theory, this low adherence to treatment could have affected our results, although we think it unlikely to have had a significant effect. For example, in the per-protocol analysis of the PROCTOR-SCRIPT trial,[15] adjuvant chemotherapy was not beneficial for patients who completed all cycles of adjuvant chemotherapy. Another potential limitation is that the EORTC 22921 trial, the I-CNR-RT trial, and the PROCTOR-SCRIPT trial all had long accrual periods, and thus may have been affected by changes in practice over time. For example, total mesorectal excision was not yet the standard of care during most of the I-CNR-RT trial, and became standard of care halfway through the EORTC 22921 trial. Lastly, the QUASAR trial was not included in our meta-analysis because we could not obtain individual patient data.

If patients with a tumour 10–15 cm from the anal verge do benefit from adjuvant chemotherapy, the question is whether fluoropyrimidine monotherapy or combination chemotherapy should be administered. No clear evidence of the superiority of fluoropyrimidine monotherapy or combination chemotherapy existed at the start of most of the included trials. Three of the trials included in this meta-analysis used fluoropyrimidine monotherapy. In 2009, results of the MOSAIC trial showed that the addition of oxaliplatin to fluorouracil and folinic acid improved disease-free survival and overall survival in patients with colon cancer.[26,43] For this reason, the CHRONICLE trial used combination chemotherapy.[16] Findings from the ADORE trial[44] showed that adjuvant FOLFOX (folinic acid, fluorouracil, and oxaliplatin) seems to be more beneficial than fluorouracil and folinic acid for patients with ypTNM stage II or III rectal cancer. The results of the CAO/ARO/AIO-04 trial[45] showed a benefit of adjuvant combination chemotherapy over fluorouracil monotherapy. Because both studies did not include an observation arm, they were ineligible for this meta-analysis. The question whether adjuvant combination chemotherapy provides a benefit compared with observation thus remains unanswered.

In conclusion, overall, fluorouracil-based adjuvant chemotherapy did not improve overall survival, disease-free survival, and distant recurrences compared with observation for patients with (y)pTNM stage II or III rectal cancer, who had an R0 resection, had a low anterior resection or an abdominoperineal resection, and had a tumour located within 15 cm of the anal verge. 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.

Contributors

AJB, MS, HP, EB, and CJHvdV analysed the data. LC, RG-J, J-FB, and CJHvdV were principal investigators of the trials included in this meta-analysis. All authors participated in the interpretation and writing of this report. All authors approved the final version before submission.

Declaration of interests

We declare no competing interests.

Acknowledgments

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