Improving colorectal cancer care: treatment and outcomes of patients with colorectal cancer

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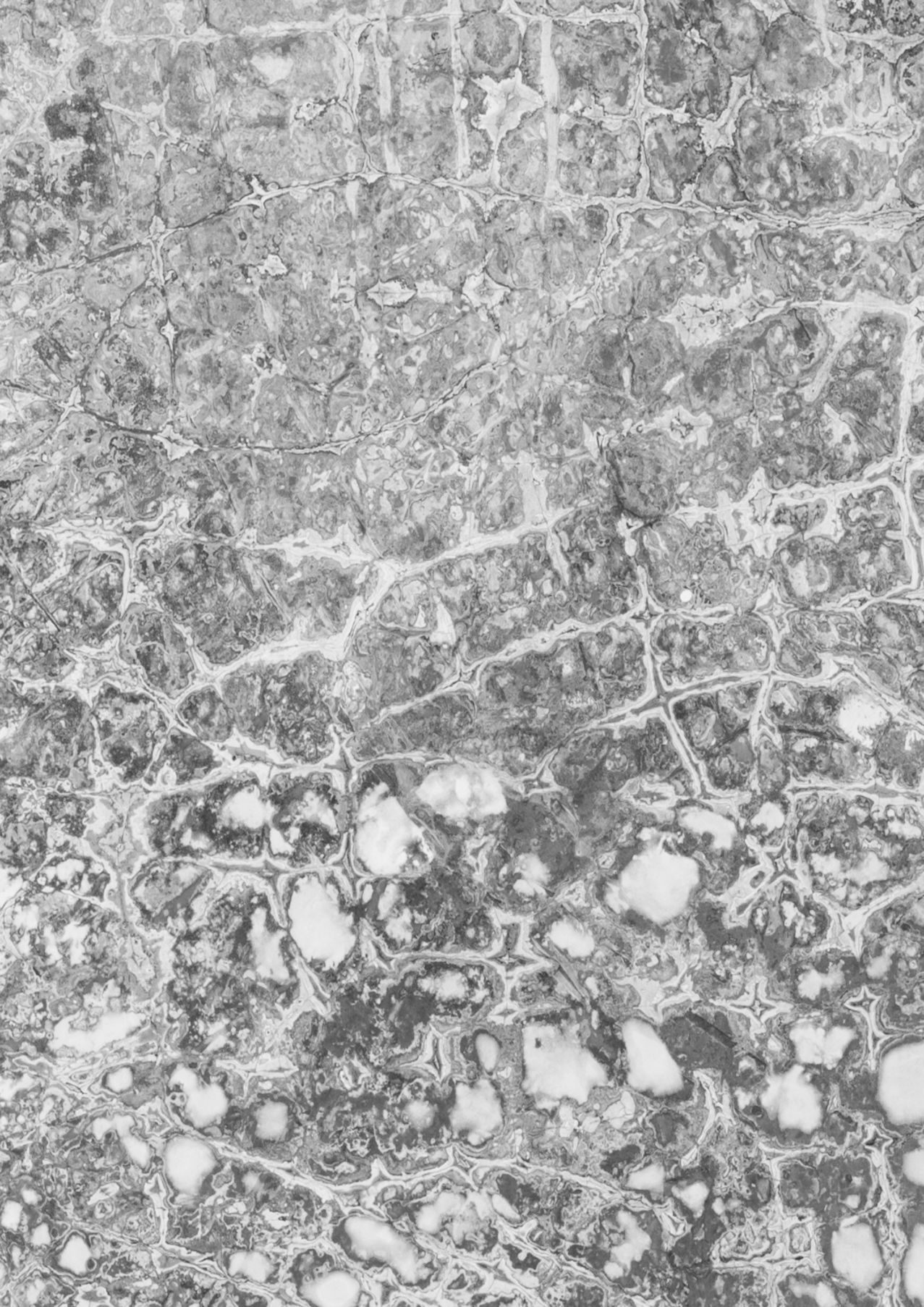

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Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomised phase III trial

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Annals of Oncology. 2015 Apr;26(4):696-701.

ABSTRACT

Background

The discussion on the role of adjuvant chemotherapy for rectal cancer patients treated according to current guidelines is still ongoing. A multicentre, randomised phase III trial, PROCTOR-SCRIPT, was conducted to compare adjuvant chemotherapy with observation for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision (TME).

Patients and Methods

The PROCTOR-SCRIPT trial recruited patients from 52 hospitals. Patients with histologically proven stage II or III rectal adenocarcinoma were randomly assigned (1:1) to observation or adjuvant chemotherapy after preoperative (chemo)radiotherapy TME. Radiotherapy consisted of 5x5 Gy. Chemoradiotherapy consisted of 25x1.8-2 Gy combined with 5-FU based chemotherapy. Adjuvant chemotherapy consisted of 5-FU/LV (PROCTOR), or eight courses capecitabine (SCRIPT). Randomisation was based on permuted blocks of six, stratified according to centre, residual tumour, time between last irradiation and surgery, and preoperative treatment. The primary end point was overall survival.

Results

Of 470 enrolled patients, 437 were eligible. The trial closed prematurely because of slow patient accrual. Patients were randomly assigned to observation (n=221) or adjuvant chemotherapy (n=216). After a median follow-up of 5.0 years, 5-year overall survival was 79.2% in the observation group and 80.4% in the chemotherapy group (hazard ratio (HR) 0.93, 95% CI 0.62-1.39; p=0.73). The HR for disease-free survival was 0.80 (95% CI 0.60-1.07; p=0.13). Five-year cumulative incidence for locoregional recurrences was 7.8% in both groups. Five-year cumulative incidence for distant recurrences was 38.5% and 34.7%, respectively (p=0.39).

Conclusion

The PROCTOR-SCRIPT trial could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy after preoperative (chemo) radiotherapy and TME on overall survival, disease-free survival, and recurrence rate. However, this trial did not complete planned accrual.

Funding

This work was supported by The Dutch Cancer Society (KWF 1999-03 and KWF 2003-16), the Dutch Colorectal Cancer Group, and the Swedish Cancer Society. Furthermore, Roche has provided an unrestricted educational grant.

INTRODUCTION

Locoregional recurrence rates and survival have significantly improved with the introduction of total mesorectal excision (TME) for patients with rectal cancer.[1,2] Further improvements in rectal cancer treatment were made by the possibility of more accurate staging with magnetic resonance imaging (MRI), and by the use of preoperative short-course radiotherapy or long-course chemoradiotherapy.[3-6] The addition of preoperative radiotherapy to TME surgery resulted in a more than 50% decrease in locoregional recurrences. However, the combination of preoperative (chemo)radiotherapy and TME surgery did not improve overall or disease-free survival[3,5,6], although cancer-specific survival was significantly better in patients operated with a negative circumferential margin after preoperative radiotherapy.[3]

In contrast to locoregional recurrence rates, distant metastasis rates did not improve. Up to 30% of all patients treated with curative intent for localised rectal cancer will develop distant metastases[3,5], and distant metastases are still the main cause of death after rectal cancer.[7]

Adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME surgery could eradicate micrometastases. This might reduce distant metastases, resulting in improved outcomes. Currently, there is no conclusive evidence on the benefit of adjuvant chemotherapy in rectal cancer treatment after preoperative (chemo)radiotherapy followed by TME surgery, and the debate on this subject is still ongoing.[8]

With this trial, we aim to investigate the value of adjuvant chemotherapy with fluoropyrimidine monotherapy after preoperative (chemo)radiotherapy and TME surgery.

PATIENTS AND METHODS

Study design and patients

We undertook a randomised, controlled, phase III trial in 52 hospitals. Patients were randomised to observation or adjuvant chemotherapy after preoperative (chemo) radiotherapy and TME surgery. Initially, radiotherapy was given in five factions of 5 Gy and adjuvant chemotherapy consisted of 5-FU/LV (PROCTOR – **P**reoperative **R**adiotherapy and / **O**r adjuvant **C**hemotherapy combined with **T**ME surgery in **O**perable **R**ectal cancer). After a protocol amendment, chemoradiotherapy was also allowed and capecitabine was used as adjuvant treatment (SCRIPT – **S**imply **C**apecitabine in **R**ectal cancer after **I**rradiation **P**lus **T**ME).

Patients aged ≥18 years, with a rectal adenocarcinoma (below the level of S1/S2 on CT or MRI, or located within 15 cm from the anal verge measured during withdrawal of a flexible or rigid scope), who had preoperative (chemo)radiotherapy and TME surgery, (y)pTNM stage II or III, an R0 (PROCTOR and SCRIPT) or R1 (SCRIPT) resection, and who could start chemotherapy within six weeks after surgery, were eligible.

Exclusion criteria were Familial Adenomatosis Polyposis Coli, Hereditary Non-Polyposis Colorectal Cancer, active inflammatory bowel disease, DPD deficiency, and present or prior malignancies except for adequately treated basocellular carcinoma of the skin, or in situ carcinoma of the cervix uteri (PROCTOR: no prior malignancies, SCRIPT: at least ten years disease-free).

We obtained ethical approval from central and local ethics committees. All patients gave written informed consent.

Randomisation

Randomisation was carried out centrally at the datacentre of the Department of Surgery at the Leiden University Medical Centre. Patients were randomly assigned (1:1) to observation or adjuvant chemotherapy. Randomisation was computer-generated and based on permuted blocks of six, with stratification according to centre, residual tumour (R0/R1), time between last irradiation and surgery, and preoperative treatment.

Procedures

Preoperative radiotherapy consisted of 25 Gy in five fractions of 5 Gy, preoperative chemoradiotherapy of 45-50 Gy in 25 fractions(1.8-2 Gy) with 5-FU based chemotherapy. The Clinical Target Volume (CTV) included the primary tumour and the mesentery with vascular supply containing the perirectal, the presacral and the internal iliac nodes (up to the S1/S2 junction). If an abdominoperineal resection was planned, the inner and outer anal sphincter were included. A three or four beams technique was mandatory. Patients were treated in either prone or supine position.

Standardised TME surgery was carried out according to strict and controllable quality demands.[2,3] Standardised pathological examination was carried out.[9] A circumferential resection margin of ≤1 mm was considered positive. R1 resection was defined as both microscopic residual tumour and a circumferential resection margin (CRM) of ≤1 mm. Good TME surgery, including an intact mesorectum, no deep defects, no coning, and a smooth CRM, was performed in 82.7% (PROCTOR) and 66.0% (SCRIPT) of the patients.

Adjuvant chemotherapy consisted of leucovorin 20mg/m^2 immediately followed by 5-FU 425mg/m^2 by intravenous bolus injection daily for five days, repeated every four to five

weeks for six courses (Mayo regimen), or of 5-FU 500mg/m^2 followed by leucovorin 60mg/m^2 after 30 to 40 minutes by bolus intravenous injections daily, for two consecutive days every 14 days for 12 courses (Nordic regimen). After a protocol amendment, adjuvant chemotherapy consisted of eight courses of 1.250 mg/m^2 oral capecitabine twice daily (days 1-14 every 21 days).

All Dutch patients were assessed every 3 months after surgery during the first 2 years and annually afterwards. All Swedish patients were assessed at 1 and 3 years or every six months for three years according to the COLOFOL trial.[10] Locoregional recurrence was defined as a recurrence within the pelvic, anastomotic, or perineal area. Distant recurrence was defined as tumour growth in any other area.

End points

Primary end point was overall survival. Secondary end points were disease-free survival, overall recurrence rate, and locoregional and distant recurrence rate separately.

Statistical analyses

A total of 840 patients (294 events) was needed to detect an improvement in 5-year overall survival from 60% to 70% (alpha 0.05, two sided; power 0.90).

All analyses were carried out by intention-to-treat. A per-protocol analysis was done on patients in the observation group who survived at least 210 days (to avoid immortal time bias), and eligible patients that completed all chemotherapy cycles. A sensitivity analysis including all randomised patients was carried out on the primary end point.

Overall survival was defined as time to death (any cause), or 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 locoregional, distant or overall recurrence was defined as time to the specific recurrence, or end of follow-up (censored).

Overall survival and disease-free survival curves were calculated with the Kaplan-Meier method. The hazard ratios (HR) and their 95% confidence intervals (CIs), and the cumulative incidence of recurrences, were calculated with Cox proportional hazards model. In order to determine differences between PROCTOR and SCRIPT, an interaction term between randomisation and study part was used.

Statistical analyses were carried out using IBM SPSS Statistics (20.0). A p-value of ≤0.05 was considered statistically significant.

RESULTS

Between 1 March 2000 and 1 January 2013, 470 patients were included, of whom 33 were incorrectly randomised. Therefore, 437 patients (309 Dutch and 128 Swedish patients) were eligible for analyses. The trial was finally closed due to poor patient accrual without reaching the intended inclusion. Preoperative staging with CT or MRI was done in 50.6% in the PROCTOR part, while in the SCRIPT part 74.5% had a pelvic MRI scan. The median time from surgery to the start of adjuvant chemotherapy was 6.0 weeks.

Of the incorrectly randomised patients, 15 did not have ypTNM stage II or III, 13 received TME surgery without preoperative (chemo)radiotherapy, 4 had a tumour not located within 15 cm from the anal verge, and 1 received long-course radiotherapy without chemotherapy (supplementary Figure S1). Of the eligible patients, 221 patients were randomised to observation and 216 patients were randomised to adjuvant chemotherapy. The trial profile is demonstrated in supplementary Figure S1. Patient characteristics were equally distributed between the two groups (Table 1).

Table 1. Patient characteristics

Characteristics	Total (*n* = 437)	Observation (*n* = 221)	Chemotherapy (*n* = 216)
Age (years)	61.08 ± 9.03	61.08 ± 9.13	61.13 ± 8.94
Gender			
Male	270 (61.8)	139 (62.9)	131 (60.6)
Female	167 (38.2)	82 (37.1)	85 (39.4)
Preoperative treatment			
Radiotherapy	376 (86.0)	193 (87.3)	183 (84.7)
Chemoradiotherapy	61 (14.0)	28 (12.7)	33 (15.3)
Type of resection			
LAR	275 (62.9)	142 (64.3)	133 (61.6)
APR	146 (33.4)	70 (31.7)	76 (35.2)
Hartmann	16 (3.7)	9 (4.1)	7 (3.2)
Tumour location from anal verge			
< 5 cm	113 (25.9)	51 (23.1)	62 (28.7)
5 – 9.9 cm	139 (31.8)	75 (33.9)	64 (29.6)
≥ 10 cm	168 (38.4)	83 (37.6)	85 (39.4)
Unknown	17 (3.9)	12 (5.4)	5 (2.3)
CRM			
Negative	409 (93.6)	208 (94.1)	201 (93.1)
Positive	19 (4.3)	8 (3.6)	11 (5.1)
Unknown	9 (2.1)	5 (2.3)	4 (1.9)
Residual tumour			
R0	418 (95.7)	213 (96.4)	205 (94.9)
R1	19 (4.3)	8 (3.6)	11 (5.1)
(y)pTNM			
II	71 (16.2)	32 (14.5)	39 (18.1)
III	366 (83.8)	189 (85.5)	177 (81.9)

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

In the chemotherapy group, 73.6% (*n*=159) completed all chemotherapy cycles, 20.8% did not, while 4.6% never started chemotherapy. Information on chemotherapy compliance was missing in 0.9% (supplementary Figure S1). In 14.8%, toxicity was the reason to end chemotherapy. Capecitabine was used in 65.3% of the patients. The remaining 34.7% received 5-FU/LV (37.3% Mayo regimen, 48.0% Nordic regimen, 14.7% unknown regimen).

Follow-up was completed until 27 June 2014. Median follow-up of surviving patients was 5.0 years (range 0.02 – 13.12 years).

Overall survival

A total of 95 patients died. Five-year overall survival was 79.2% in the observation group and 80.4% in the chemotherapy group (HR 0.93, 95% CI 0.62-1.39; *p*=0.73; Figure 1A).

The per-protocol analysis demonstrated an HR of 0.77 for overall survival (95% CI 0.49-1.21; *p*=0.26). A sensitivity analysis of all patients showed an HR of 0.94 (95% CI 0.64-1.38; *p*=0.75). The effect of adjuvant chemotherapy on overall survival did not differ between PROCTOR and SCRIPT ($p_{interaction}$=0.54).

Disease-free survival

No statistically significant difference in disease-free survival was observed. Five-year disease-free survival was 55.4% for the observation group and 62.7% for the chemotherapy group (HR 0.80, 95% CI 0.60-1.07; *p*=0.13; Figure 1B). In the per-protocol analysis, the HR was 0.77 (95% CI 0.55-1.06; *p*=0.11).

There was no difference in the effect of adjuvant chemotherapy between PROCTOR and SCRIPT ($p_{interaction}$=0.49).

Recurrences

In total, there were 157 recurrences. At 5 years, the cumulative incidence for overall recurrences was 40.3% in the observation group and 36.2% in the chemotherapy group (HR 0.88, 95% CI 0.64-1.20; *p*=0.43). Similar results were found in per-protocol analysis (HR 0.87, 95% CI 0.61-1.22; *p*=0.41).

The 5-year cumulative incidence for locoregional recurrences was 7.8% in the observation group versus 7.8% in the chemotherapy group (HR 1.17, 95% CI 0.55-2.50; *p*=0.69), whereas this amounted to 38.5% and 34.7%, respectively for distant recurrences (HR 0.87, 95% CI 0.63-1.20; *p*=0.39; Figure 2). The per-protocol analysis showed an HR of 1.24 for locoregional recurrences (95% CI 0.56-2.76; *p*=0.60) and 0.85 (95% CI 0.59-1.21; *p*=0.36) for distant recurrences.

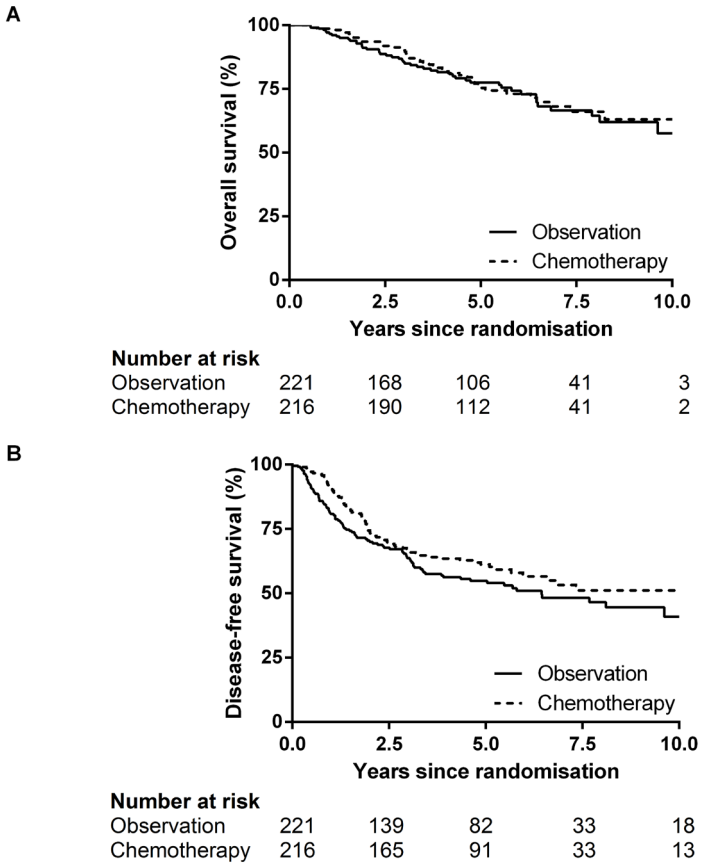

Figure 1. a. Overall survival. b. Disease-free survival

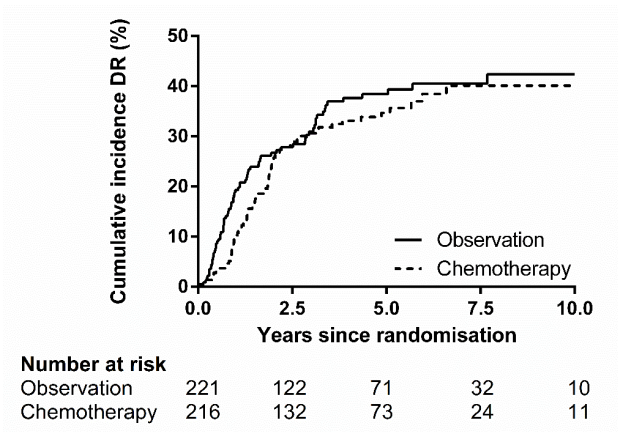

Figure 2. Cumulative incidence distant recurrence

DISCUSSION

After a median follow-up of 5 years, the PROCTOR-SCRIPT trial could not demonstrate a significant benefit in overall survival for adjuvant chemotherapy after preoperative (chemo)radiotherapy and TME surgery in ypTNM stage II and III rectal cancer patients. Furthermore, no significant differences were demonstrated in disease-free survival, and recurrence rates.

Now that locoregional recurrence rates decreased, the focus of rectal cancer treatment is on reducing distant metastases. However, the debate on the role of adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and TME surgery is still ongoing. On the contrary, the advantage of adjuvant chemotherapy for stage III colon cancer has been clearly proven.[11-14]

Although colon and rectal tumours have histological similarities, and are in anatomical continuity, tumour biology is not the same.[15] Nevertheless, several guidelines recommend the use of adjuvant chemotherapy for rectal cancer[16-18] based on extrapolation from experience with colon cancer. In contrast, the Dutch guidelines state that there is no indication for adjuvant chemotherapy.[19]

These differences in adjuvant chemotherapy use can be explained by the fact that no conclusive evidence exists for patients treated with preoperative (chemo)radiotherapy and TME surgery.

Adjuvant chemotherapy appears to be effective in patients who neither received preoperative (chemo)radiotherapy nor standardised surgery. One study then often referred to is a Japanese trial demonstrating a benefit in disease-free and overall survival of uracil-tegafur in stage III rectal cancer patients who underwent standardised mesorectal excision, including selective lateral pelvic lymphadenectomy. None of the patients underwent preoperative radiotherapy.[20] Further, a Cochrane review of 21 trials showed a risk reduction of 17% on overall survival and 25% on disease-free survival among patients who received adjuvant chemotherapy.[21] It must be taken into account that none of the trials performed standardised TME surgery, that no standardised definition of rectum was used, and that only two of the included studies administered preoperative (chemo)radiotherapy. One of these two trials, the QUASAR, found a small improvement in survival for patients with rectal cancer who received adjuvant chemotherapy. However, of all rectal cancer patients, only 21% received preoperative radiotherapy.[22] The second trial, the EORTC 22921 trial, did not demonstrate a benefit of adjuvant chemotherapy after 5 years.[23]

The results of the present trial are consistent with results of three trials investigating the role of adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery[6,24,25], and support the conclusions made by Bujko et al. in a systematic review.[8] First, the EORTC 22921 trial did not demonstrate any clinically relevant nor statistically significant benefit of adjuvant 5-FU/LV in overall survival, disease-free survival, or recurrence rates. Ten-year overall survival was 48.4% in the observation group and 51.8% in the chemotherapy group.[6] Secondly, the CHRONICLE trial randomised 113 patients who received preoperative chemoradiotherapy between observation and adjuvant CAPOX. This trial closed prematurely because of poor patient accrual. After 3 years, no significant differences in disease-free and overall survival could be detected.[25] Thirdly, an Italian trial, randomised patients between observation and adjuvant 5-FU/LV after preoperative chemoradiotherapy and surgery, and did also not find differences in overall survival and distant recurrences after 10 years.[24]

The lack of effect of adjuvant chemotherapy in rectal cancer has often been attributed to poor compliance. In the current trial, 73.6% of the patients randomised to chemotherapy completed all cycles. In comparison, chemotherapy compliance was 43% in the EORTC 22921 trial, 48% in the CHRONICLE trial, and about 55% received three to six chemotherapy cycles in the Italian trial.[6,23-25] The difference in chemotherapy compliance can probably be explained by the fact that we randomised patients postoperatively, resulting in a selected group fit enough to start chemotherapy, although the CHRONICLE trial also randomised postoperatively. However, CHRONICLE used combination chemotherapy, which can be a possible explanation for this difference. Despite the relatively high compliance rate in our trial, no differences between the observation group and the chemotherapy group could be demonstrated.

In the current trial, fluoropyrimidine monotherapy was used as adjuvant treatment, because no clear evidence on the benefit of combination chemotherapy existed at the start of our trial. Meanwhile, the MOSAIC trial demonstrated a benefit in disease-free and overall survival of combination chemotherapy for colon cancer.[14] In the South Korean population of the recently published phase two ADORE trial, there seems to be a benefit of adjuvant FOLFOX over 5-FU/LV for patients with ypTNM stage II or III rectal cancer.[26] Besides, the results of the CAO/ARO/AIO-04 trial are awaited for the effect of combination chemotherapy on disease-free survival.[27]

This trial has some limitations. The intended inclusion of 840 patients was not reached due to poor patient accrual. Many patients and clinicians had preference for either observation or chemotherapy which resulted in a lower participation rate than anticipated. Furthermore, 5-year overall survival was better than calculated. Therefore, we would have required a larger number of events for an adequate power. The lack of

statistical power can be a possible explanation for the fact that differences between the observation and the chemotherapy group could not be detected, as for example the 7% difference in disease-free survival which might have been significant with appropriate statistical power.

Moreover, different follow-up schedules are used in the Netherlands and Sweden, which could have influenced disease-free survival and recurrence rates. In addition, the trial was amended: adjuvant chemotherapy changed from 5-FU/LV (PROCTOR) to capecitabine (SCRIPT), and patients received preoperative chemoradiotherapy or radiotherapy (SCRIPT) instead of radiotherapy only (PROCTOR). Given the similarity in study design, the similar efficacy of 5-FU/LV and capecitabine, and the fact that no differences in treatment effect existed between PROCTOR and SCRIPT, it is unlikely that these changes have influenced overall outcomes significantly.

Still considerable debate exists on the definition of the rectum, with regard to distance from the anal verge and location of peritoneal reflection. Possibly, upper rectal tumours are more similar to low sigmoid tumours that benefit from adjuvant chemotherapy. Furthermore, it would be interesting to investigate the role of adjuvant chemotherapy for stage III rectal cancer. We will perform an individual patient data meta-analysis including data of European trials to investigate if subgroups of patients benefit from adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery. Moreover, we will try to identify prognostic or predictive biomarkers in tumour material of patients included in our trial, which will give insight in tumour prognosis, and can be the basis for tailor-made treatment.

In conclusion, with the PROCTOR-SCRIPT trial we could not demonstrate a significant benefit of adjuvant chemotherapy with fluoropyrimidine monotherapy regarding overall survival, disease-free survival, and recurrence rates after preoperative (chemo) radiotherapy and TME surgery in ypTNM stage II and III rectal cancer patients. However, this trial did not complete planned accrual.

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SUPPLEMENTARY DATA

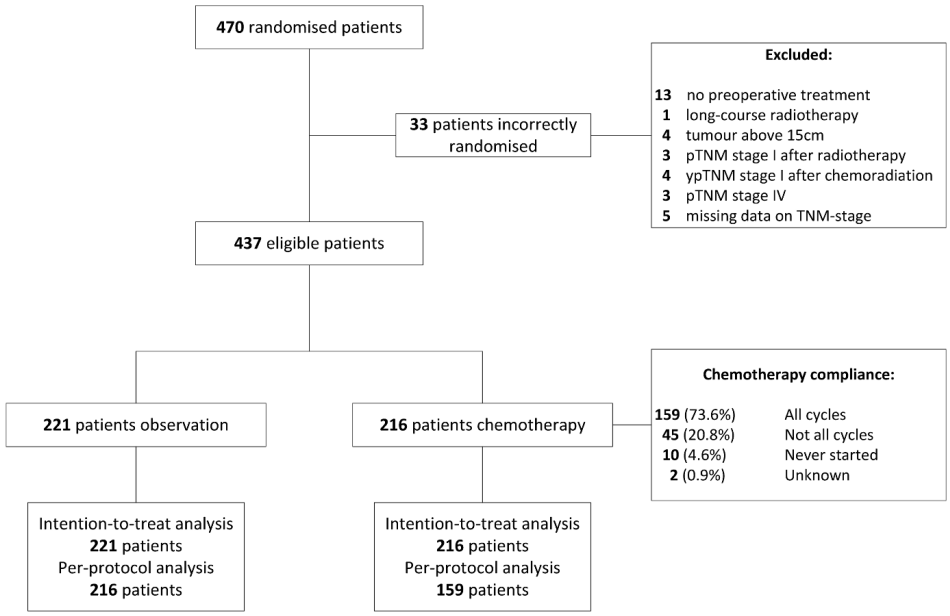

Figure 1. CONSORT diagram