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ORIGINAL ARTICLE

Adjuvant chemotherapy in colorectal cancer: A joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group

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Abstract

Due to uncertainties regarding clinically meaningful gains from adjuvant chemotherapy after colorectal cancer surgery, several Nordic Groups in the early 1990s initiated randomised trials to prove or reject such gains. This report gives the joint analyses after a minimum 5-year follow-up. Between October 1991 and December 1997, 2 224 patients under 76 years of age with colorectal cancer stages II and III were randomised to surgery alone (n = 1 121) or adjuvant chemotherapy (n = 1 103) which varied between trials (5FU/levamisole for 12 months, n = 444; 5FU/leucovorin for 4–5 months according to either a modified Mayo Clinic schedule (n = 262) or the Nordic schedule (n = 397). Some centres also randomised patients treated with 5FU/leucovorin to ± levamisole). A total of 812 patients had colon cancer stage II, 708 colon cancer stage III, 323 rectal cancer stage II and 368 rectal cancer stage III. All analyses were according to intention-to-treat. No statistically significant difference in overall survival, stratified for country or region, could be found in any group of patients according to stage or site. In colon cancer stage III, an absolute difference of 7% (p = 0.15), favouring chemotherapy, was seen. The present analyses corroborate a small but clinically meaningful survival gain from adjuvant chemotherapy in colon cancer stage III, but not in the other presentations.

In 1990, a US National Cancer Institute (NCI) consensus conference recommended adjuvant 5-fluorouracil (5-FU) plus levamisole for twelve months for stage III colon cancer [1]. The recommendation was based upon favourable outcome in treated patients in one small study [2] and one large Intergroup trial (INT-0035) [3]. In the Intergroup trial, which included 929 patients with stage III disease, overall survival after 6.5 years of follow-up improved from 40% to 51% [4]. No corresponding benefit was seen in stage II [5]. After the consensus statement, six trials, all randomising patients between surgery alone or surgery plus six months of 5-FU plus leucovorin, stopped patient inclusion. Those trials, including a total of 2 203 eligible patients also showed a better disease-free and overall survival in stage III patients randomised to chemotherapy [6–9]. No clear benefit was seen in stage II when the results of three trials were pooled [10]. However, for the same sample size a trial in stage II will have less statistical power than a trial in stage III, due to the lower event rate. A large pooled analysis

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(1 565 patients with stage II and 2 255 patients with stage III disease) of four NSABP trials indicated that the relative reduction of mortality risk among stage II patients was at least equal to that observed among stage III patients [11]. In one of these trials, including 1 166 patients in stages II+III, the survival benefits associated with chemotherapy at 5 years were no longer present at 10-year follow-up [12].

There is less knowledge of benefits from postoperative chemotherapy in rectal cancer [13]. In small randomised trials [14–16] postoperative chemo(radio)therapy improved survival to the same extent as chemotherapy in stage III colon cancer and this was also recommended therapy in an NCI announcement [17].

The consensus statement in colon cancer in 1990 [1] and the follow-up statement for rectal cancer in 1991 [17] had a great impact on clinical practice worldwide, although some European groups wanted more documentation prior to the general acceptance of routine adjuvant therapy for colon stage III disease. Thus, several randomised trials, still including a surgery alone group, were initiated.

A Dutch group randomised 1 029 patients with colorectal cancer stages II+III. After a median follow-up of four and a half year, a significant reduction in odds of death was observed for those treated with twelve months of 5-FU/levamisole. The favourable effects were seen in colon cancer stages II and III but not in rectal cancer [18].

A UK collaborative group designed two parallel trials (QUASAR, Quick and Simple and Reliable), one of which compared a surgery alone group with adjuvant 5-FU/leucovorin (QUASAR Uncertain) whereas the other trial compared different 5-FU-based regimens. In the first analyses of the QUASAR Uncertain trial including 3 238 patients (91% stage II, 71% colon cancer), the risk of death with chemotherapy vs control was 0.88 (95% confidence intervals (C1) 0.75–1.05; $p = 0.15$) [19]. In the QUASAR Certain trial, no difference was seen between either a high dose or a low dose of leucovorin with 5-FU. Similarly, no benefit was seen from the addition of levamisole [20].

In the Nordic countries in the early 1990s, there was also widespread scepticism of sufficient benefit from adjuvant chemotherapy for colon cancer stage III. Three separate trials were initiated early on, in Denmark, in Norway and in the Stockholm Health Care Region in Sweden. The trials included patients with colorectal cancer stages II+III. The adjuvant treatment was 5-FU/levamisole for 12 months in the Danish and Norwegian trials, whereas the Stockholm trial employed a modified Mayo Clinic 5-FU/leucovorin-schedule for 4 months, with or without levamisole. Further discussions within the Scandinavian countries led to a proposal to make a joint effort with the overall aim of proving or refuting clinically meaningful gains from adjuvant chemotherapy in the various stages and sites of colorectal cancer. Some of the trials then had a pragmatic design, so that any results would probably be relevant for the general population considered for treatment. The various groups could opt for different cytostatic regimens, but all were required to randomise 50% of the patients to surgery alone and 50% to surgery and postoperative chemotherapy. An interim analysis of overall survival according to randomisation (surgery or surgery plus any chemotherapy) was performed after 1 000 patients were included with a minimum of one year's follow-up. The interim analysis did not reveal any difference between the survival curves, and the trials continued until the planned number of patients were included. This report gives the joint results of the trials after a minimum follow-up of 5 years.

Patients and methods

Patients

Patients curatively resected for stage II or stage III adenocarcinoma of the colon or rectum were eligible for randomisation provided they were under 76 (75 in Norway and Denmark) years of age. Informed consent was obtained according to each centre's regulations. Exclusion criteria varied slightly between trials, but patients who had another malignancy except squamous cell carcinoma of the skin and cervical carcinoma stage 0, had received previous chemotherapy or radiotherapy (Norway and Denmark only), had severe cardiopulmonary disease and no major laboratory abnormalities were excluded. Early randomisation and initiation of the adjuvant therapy after surgery were emphasised in all trials, but different time limits were set (Norway: treatment start within 42 days; Denmark: randomisation within 30 days, treatment start within 40 days; Stockholm treatment start within 10 weeks; rest of Sweden: as early as possible, or preferably within 49 days).

All studies were approved by the regional research ethics committees and informed consent was obtained from all participants.

Treatment

At each centre, 50% of the patients were randomised to surgery alone (group A) or surgery followed by chemotherapy (groups B–D). The various groups (and centres in the Uppsala-Örebro region) could choose between one of a limited number of regimens. The choice can be seen in Table I. One

Table I. Number of randomised patients per country and Health Care Region in Sweden.

Region/country	Inclusion dates month/year	Randomised					
		Surgery (A)	5FU+levamisole (B)	5FU+leucovorin (C)		5FU+leucovorin+levamisole (D)	
				Mayo (C1)	Nordic (C2)	Mayo (D1)	Nordic (D2)
Stockholm	10/91–12/97	**197**		**99**		**98**	
Rest of Sweden	03/93–12/96	**545**	**63**	**65**	**246**		**151**
Northern		72		65			
Uppsala/Örebro		293	34		174		70
South-Eastern		103			51		49
Western[a)]		31	29				
Southern		46			21		32
Sweden Total		**742**	**63**	**164**	**246**	**98**	**151**
Denmark	02/92–12/96	168	167				
Norway	01/93–10/96	211	214				
TOTAL				**164**	**246**	**98**	151
			444	**410**		**249**	
		1 121			**1 103**		

[a)] Only included patients in stage III.

alternative (group B) was 5-FU plus levamisole according to the original Moertel scheme [3] with 5-FU as a push injection (450 mg/m^2) daily for 5 consecutive days followed from day 28 onwards by 5-FU (450 mg/m^2) given once weekly for 48 weeks. Levamisole was given in 3 daily doses of 50 mg during 3 days of the loading course, and repeated every 2 weeks for 52 weeks. A second alternative was 5-FU with leucovorin, either according to a modified Mayo Clinic schedule (group C1) with 5-FU 425 mg/m^2 iv push followed 30 minutes later by leucovorin 20 mg/m^2 for 5 consecutive days every 4 weeks for 4 courses, or according to the Nordic schedule (group C2) with 5-FU 500 mg/m^2 iv push and leucovorin 60 mg/m^2 30 minutes later days 1 and 2 every 14 days for 10 courses. As a third alternative, the 5-FU/leucovorin schedule could be given either alone or together with levamisole (groups D1 and D2) (50 mg $\times$ 3 days every 14 days) in a randomised way. The number of patients randomised to the various schedules in the different countries/Health Care Regions in Sweden is shown in Table I.

Toxicity was graded according to the WHO criteria. In case of grade III or IV mucositis, diarrhoea or bone marrow depression, the 5-FU dose was reduced by 20% after complete recovery. If the toxicity continued, the dose could be further reduced by 20% or treatment stopped. The toxicity grading was not prospectively recorded on case record forms by all groups, and, thus, no meaningful analyses can be done in this joint analysis.

The follow-up routines varied between the trials, and some groups did not consider disease-free survival as a secondary end-point. This end point, consequently, can only be evaluated for a subset of the patients, and is not presented here.

Statistical analysis

Time to death, irrespective of the cause, calculated from the date of randomisation, was the main end point of the current study. To be able to detect a 10% difference in mortality from 50% to 60% with a power of 80%, approximately 400 patients per treatment group had to be included (2-tailed test, $p < 0.05$). It was decided to include a total of 2 200 patients, based upon an expectation that slightly more patients would have stage III than stage II disease and that about 2/3 of the patients would present with colon cancer. Thus, with 2 200 patients we estimated that about 800 patients could be included in both colon cancer stage II and stage III.

Randomisation was performed by a national (in Sweden and Norway regional) coordinating centre, and stratification was done according to stage (II or III), site (colon or rectum) and hospital. All analyses were according to intention-to-treat. Simple descriptive tests of pre-treatment characteristics were used. Survival was analysed with log-rank test. Hazard ratios were calculated, stratified for country or health care region.

Results

Population characteristics and treatment

In total, 2 224 patients were randomised. The numbers in the various groups according to randomisation are shown in Table I. Of these, insufficient data were retrievable from 13 patients (0.6%), 4 in the surgery alone group and 9 in the chemotherapy groups. All these patients were also ineligible and were withdrawn by the investigator soon after randomisation. Thus, the analyses are based upon

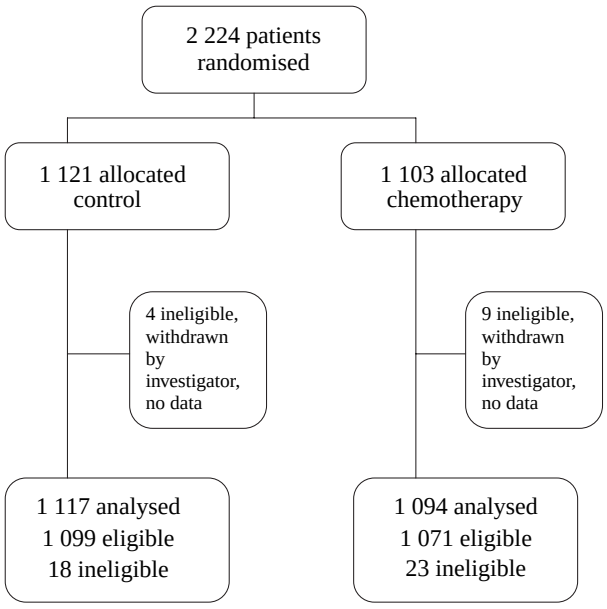

Figure 1. Trial profile according to the Consort statement at http://www.consort-statement.org/statement.html.

2 211 patients (Figure 1). Including the 13 patients who could not be analysed, a total of 54 patients (2.4%) (22 surgery alone, 32 chemotherapy) were ineligible for the following reasons: Stage I, 20 patients; non-radical surgery or metastatic disease, 18 patients; age 76 or more, 11 patients; previous malignancy, 4 patients and no adenocarcinoma, 1 patient.

Age and sex distribution were similar in the randomisation groups (Table II). The table also shows the distribution according to tumour site and stage. The distributions were similar between the surgery alone group and the chemotherapy all group.

Randomisation was performed after a median of about 30 days, but with a wide range (Table III). This variability, however, was similar between the randomisation groups. Six per cent of the patients randomised to chemotherapy did not start any therapy. A similar proportion received chemotherapy in the surgery alone group. Those who started therapy, irrespective of randomisation group, did so after a median of 49 days.

Overall, 67% of the patients who started chemotherapy received the planned number of treatment courses (52 weeks in group B, 4 courses in C1 and D1 and 10 courses in C2 and D2). This proportion was lower (55%) in those randomised to 5FU/levamisole. Dose reductions or delays of the treatments given were rather infrequent, but occurred more frequently in patients randomised to 5FU/levamisole (no data from Denmark) or levamisole with 5FU/leucovorin (22–24%) compared with those randomised to 5-FU/leucovorin alone (7%).

Survival

Overall survival according to site and stage in all randomised patients is shown in Figure 2. The 5-year overall survival, stratified for country or region, for each of the sites and stages is shown in Table IV. It can thus be seen that there was no statistically significant survival benefit in either stratum. An absolute survival difference at 5 years of 7% was, however, detected in colon stage III ($p = 0.15$). No significant between-study heterogeneity in the effect of treatment was observed for overall survival.

Toxicity

Toxicity was not specifically addressed in this joint analysis of the trials. However, deaths during the first 6 (or 12) months after randomisation did not differ statistically significantly between randomisation groups, indicating that there was no increase in the number of toxic deaths.

Table II. Characteristics of randomised and analysed patients.

	Treatment group				
Variable	Surgery alone	Surgery and 5FU+levamisole	Surgery and 5FU+leucovorin	Surgery and 5FU+ leucovorin+levamisole	Chemotherapy All
Age - year					
Median	64	62	66	65	66
Range	29–77	42 –75	30–78	22–77	22–77
Sex – number (%)					
Male	599 (54)	238 (54)	238 (58)	137 (55)	613 (56)
Female	518 (46)	202 (46)	169 (42)	110 (45)	481 (44)
Site and stage–no					
Colon, stage II	401	160	154	97	411
Colon, stage III	364	136	131	77	344
Rectum, stage II	163	63	65	32	160
Rectum, stage III	189	81	57	41	179

Table III. Treatment in randomised and analysed patients.

Variable	Treatment group				
	Surgery alone	Surgery and 5FU+levamisole	Surgery and 5FU+leucovorin	Surgery and 5FU+ leucovorin+levamisole	Chemotherapy all
Days from surgery to randomisation					
Median	28	27	31	32	31
Range	4–124	7–102	5–160	6–96	5–160
Randomised within 30 days	741	381	211	104	696
31–42 days	178	27	92	51	170
43–49 days	78	13	44	38	95
50+ days	120	19	60	54	133
Started adjuvant treatment					
Yes	56 (5%)	417	379	232	1 028
No	1 060	21 (5%)	28 (7%)	15 (6%)	64 (6%)
Days from surgery to start of therapy*					
Median		40	51	55	49
Range		12–112	16–164	18 –112	12 –164
Started within 42 days		169 (67%)	137 (36%)	68 (29%)	374 (43%)
43–49 days		39	48	21	108
50–56 days		17	44	30	91
57+		29 (11%)	150 (40%)	113 (49%)	292 (34%)
Received a complete number of courses*		139 (55%)	278 (73%)	162 (70%)	579 (67%)
Dose reduction/delays*					
No		194 (76%)	353 (93%)	181 (78%)	728 (84%)
Yes		60	26	51	137

*No data for 163 patients in the 5FU+levamisole group from Denmark.

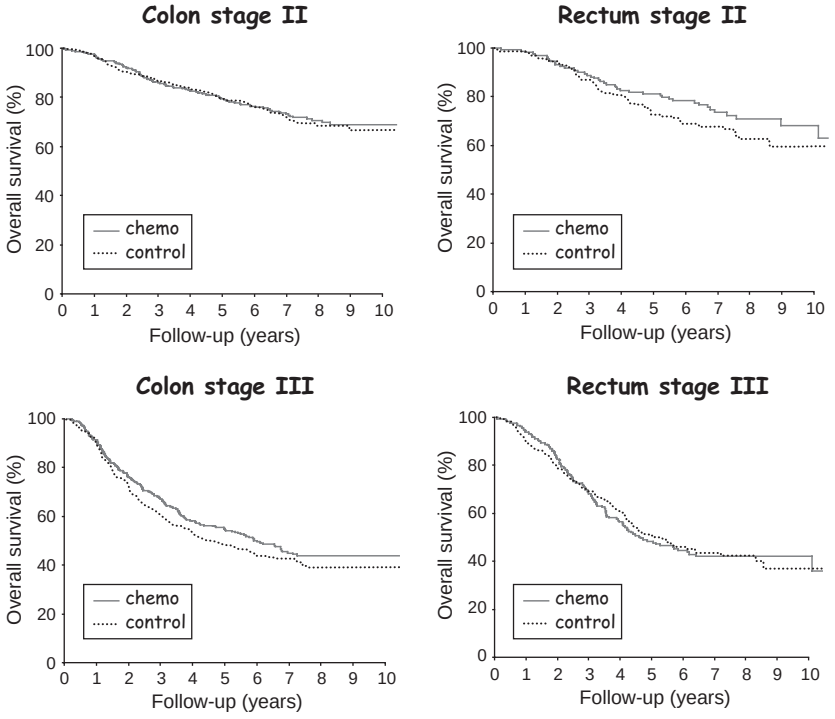

Figure 2. Overall survival according to site and stage. Number of patients and p-values, stratified for country or health care region, is shown in Table IV.

Table IV. 5-year overall survival according to site and stage.

		Number of patients	Surgery	Surgery+chemotherapy	p-value[a)]
Colon stage	II	812	79±2%	79±2%	.81
	III	708	48±3%	55±3%	.15
Rectum stage	II	323	73±4%	81± 3%	.09
	III	368	51±4%	48±4%	.91

[a)]Stratified for country or health care region.

Discussion

The immediate reflection from the results of the joint analyses of the Scandinavian trials is that they contradict previous knowledge of a proven survival gain from adjuvant chemotherapy in colon cancer stage III. However, the results of the Scandinavian trials do not differ in any significant way from previous experience. This is illustrated in Figure 3, where the hazard ratios (and 95% confidence intervals) for death from any cause are compared with those of seven randomised trials included in a recent pooled analysis [21]. The 5-year overall absolute survival benefit was 7% in the pooled analysis (43% high-risk stage II, 57% stage III) and 7% (100% stage III) in the Scandinavian trials. Furthermore, combining colon cancer stages II (low and high risk, 53% of the patients) and III in the Scandinavian trials also failed to reveal any significant difference from the pooled analysis (data not shown).

Even if the pooled analysis by Gill et al. [21] is not a meta-analysis of all available evidence, it still gives a good estimate of the survival gain seen after 6–12 months of 5FU-based chemotherapy in that it included all seven major trials reported between 1989 and 1995. Since the Dutch trial, including about 400 patients in colon cancer stage III (about 330 in stage II), showed a 12% benefit (8% in stage II), i.e. slightly above the 7% gain seen in the pooled analysis of a total of 3 351 patients (1 862 patients in stage III, estimated gain 12–15%), and the present trial show a gain of 7% in stage III, a joint analysis of all 'modern' trials would indicate that there is an absolute gain in 5-year survival of about 10–12% in colon cancer stage III from adjuvant 5FU-based chemotherapy.

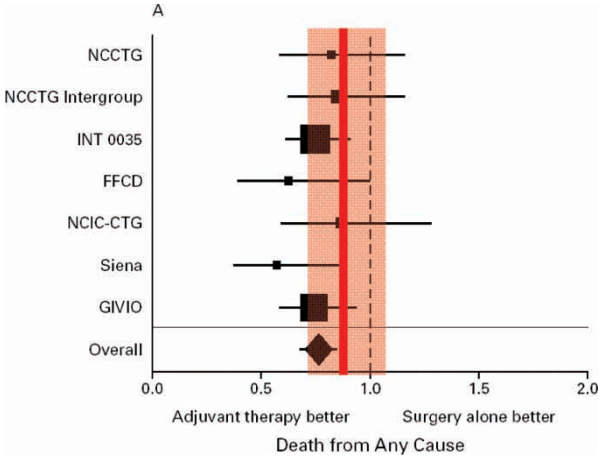

Figure 3. Hazard ratios (and 95 per cent confidence intervals) for death from any cause in 7 previous trails (pooled in [21]) and in the present studies of colon cancer stage III (thick bar and shaded area).

In colon cancer stage II, the IMPACT B2 analyses of 5 trials, including 1 016 patients, showed a non-significant 2% absolute gain from 5FU/leucovorin [10]. When the results of those trials and 4 trials using 5FU/levamisole were analysed, a non-significant trend for a survival gain from adjuvant therapy was seen (RH = 0.86, 95% CI, 0.73–1.01, p = 0.07) [22]. A similar trend was seen in the largest trial performed so far [19]. A recent meta-analysis of three Asian trials using a peroral fluoropyrimidine with mitomycin-C also reported a small benefit in node-negative colorectal cancer [23]. Analyses of several of the previous trials have thus indicated that there is a gain in node-negative colon cancer which, in relative terms, appears to be similar to that seen in node-positive cancer [11,21]. The American Society of Clinical Oncology, however, could not find direct evidence from the literature to support routine use of adjuvant therapy for colon cancer stage II [24]. We agree with their conclusion; even if a statistically significant survival difference may show up in an analysis of the evidence from all randomised trials completed so far, including the Scandinavian trials, the absolute gain is probably too small to be used routinely for the entire group of stage II patients.

The analyses presented here can be regarded as a meta-analysis of overall survival of several randomised trials run in parallel. All meta-analyses face the problem of heterogeneity between the trials. This heterogeneity is less than in most other meta-analyses, since efforts were made to apply similar inclusion and exclusion criteria. Even so, some important differences were present between the trials. Test for heterogeneity of the results between the trials did not reveal any statistically significant difference, thus indicating that the differences between the trial designs do not invalidate the overall results and conclusions.

One difference between the trials concerned the chemotherapy regimen. In the trials where a survival benefit has been shown for colon cancer stage III patients, either the 12-month Moertel scheme, the 6-month Mayo clinic or Machover regimen or the 10-month Roswell Park regimen have been used [2,3,5,7,11,18,25,26]. Since the 5-FU/leucovorin treatment (the addition of levamisole to 5-FU/leucovorin is likely irrelevant [20,27]) in the Scandinavian trials was only given for 4–5 months, only about 40% of the patients received a treatment that previously has resulted in a survival benefit as adjuvant treatment. There was, however, no indication that the difference between controls and chemotherapy treated patients was greater in patients randomised at centres using 5-FU/levamisole (about 890 patients randomised) compared to centres using 5-FU/leucovorin ($\pm$levamisole, about 1 340 patients randomised). This lack of difference according to schedule was found also when analysing only colon cancer stage III patients.

The Mayo Clinic 6-month schedule has been the most commonly used 5-FU/leucovorin schedule in the adjuvant trials, and was extensively used as a reference regimen in palliative trials until combinations of drugs turned out to be superior [28,29]. A number of different 5-FU/leucovorin schedules, among them the Nordic schedule, has been used. In metastatic disease, they have all yielded approximately the same results, with objective responses between 15 and 35% and an overall survival of about 12 months. The Nordic schedule does not differ in this respect from any of the other 5-FU/leucovorin schedules, based upon the results of several randomised multicentre trials [30–32], but it has never been compared up front with any of the other schedules. A number of factors are relevant for the anti-tumour effects of a chemotherapy schedule. The planned total dose of 5-FU in the first three months of adjuvant therapy was in one study [33] of greatest relevance for outcome, with the most favourable outcome if the dose exceeded 10 g. The Mayo Clinic schedule gives a dose of 10.8 g and the Nordic schedule 11.9 g. Dose-intensity (mg/m^2/week) and total dose of 5-FU (mg/m^2) are probably also of great relevance, though much depends on the mode of administration (bolus, short or long infusion) and potentially also on the leucovorin dose. Whatever way we compared the schedules used here (Mayo Clinic 262 patients, Nordic 397 patients) with those reported in previous trials (planned or actually given, when reported), the dose intensity, and dose during the first 3 months [33] fall within the ranges reported by others, whereas the total 5-FU dose was generally lower. Besides, in the QUASAR certain trial, a lower dose of 5-FU (370 mg/m^2) compared to the original 425 mg/m^2 yielded similar results [20]. However, since all previous trials showing a positive survival benefit of a 5-FU/leucovorin treatment have treated patients for at least 6 months, it is possible that the 4–5 months treatments given here may be of relevance for the lack of a clear survival benefit. Twelve weeks of protracted venous infusion of 5-FU gave the same survival (as effective?, see below) as 6 months of bolus 5-FU and folinic acid in one trial [34]. The doses and dose intensities in the adjuvant trials have also been discussed by Patel et al [35].

Another difference between the trials was the time difference allowed between the day of surgery to the day of first treatment given, which was allowed to vary between 6 and 10 weeks. The actual times also varied between the trials (see Table III), although, as mentioned above, no heterogeneity could be found in the results between the trials. The median time to treatment initiation (49 days) was greater than in any trial before. Actually, in all the randomised trials showing a survival benefit, the treatments were generally initiated within 35 days, and the maximum permissible number of days was 56 [2,3,5,7,11, 18,25,26]. In one of the trials, patients who did not start treatment within the stipulated 42 days were excluded from the analyses [26]. We have limited data on the relevance of a delay of adjuvant treatment, although intuitively this may be important, at least if it is very long (any beneficial effect will of course be lost if waiting until a recurrence has occurred). When this was previously explored, no clear influence was found according to whether treatment was initiated within 20 days [5] or 28 days [18]. In most of the subsequent adjuvant trials, comparing different schedules (type of drugs, doses and treatment duration) and failing to detect any differences between schedules, longer times to randomisation and treatment initiation were allowed [20,34]. Thus, there is a danger that the conclusion drawn from these trials, namely that the treatments are equally effective is inappropriate. Actually, in one of them, overall survival was significantly inferior if treatment was initiated more than 8 weeks after surgery [36].

The fact that some patients randomised to surgery got chemotherapy and some randomised to chemotherapy never received any treatment may diminish the chances of detecting a difference, if true, in an intent-to-treat analysis. Once initiated, however, treatment was given as scheduled to a proportion of the patients that does not differ from any of the other trials with a surgery alone group [2,3,5,7, 11,18,25].

Although the total number of patients included is substantial, and much greater than in previous trials

(the QUASAR Uncertain trial included more patients), the number of patients in the various stages and sites is not that high. The target goal of 800 patients in colon cancer stage III was not reached, possibly because of a reluctance to include this stage during the latter part of the trial when more evidence of a gain was reported in the literature [4,7–9,25]. None of the individuals' trials, defining a target goal based upon power calculations (Denmark, Stockholm and Norway, altogether 800 to 1 000 patients each) reached its planned target. The trials in the rest of Sweden did not make separate power calculations, but aimed at the total number of patients, described in the Patients and Methods section, and a joint analysis.

Conclusions

In conclusion, although we did not find a statistically significant improvement of overall survival in our joint analyses, an absolute benefit of 7% at 5 years for colon cancer stage III is in accordance with previously published series (see Figure 3). Therefore, our data support the continuous use of adjuvant chemotherapy in colon cancer stage III, but not in the other presentations. In colon cancer stage II and in rectal cancer, recent analyses [11, 21–23] have indicated a statistically significant gain from adjuvant treatment, but whether these effects are sufficiently large to be recommended as routine therapy cannot be stated. Presently, combination chemotherapy appears to be more efficient than 5-FU-based therapy alone [37–39].

Acknowledgements and declarations

None of the authors have declared any conflicts of interest. The corresponding author has had full access to all the data and was responsible for the final decision to submit the paper for publication.

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