

# Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial

QUASAR Collaborative Group\*

## Summary

**Background** Standard adjuvant chemotherapy for colorectal cancer consists of fluorouracil with folinic acid or levamisole. The large QUASAR randomised trial aimed to investigate (in a two×two design) whether use of a higher dose of folinic acid or addition of levamisole to fluorouracil and folinic acid improved survival.

**Methods** Patients with colorectal cancer, without evident residual disease, were randomly assigned fluorouracil (370 mg/m<sup>2</sup>) with high-dose (175 mg) or low-dose (25 mg) L-folinic acid and either active or placebo levamisole. The fluorouracil and folinic acid could be given either as six 5-day courses with 4 weeks between the start of the courses or as 30 once-weekly doses. Levamisole (50 mg) or placebo was given three times daily for 3 days repeated every 2 weeks for 12 courses. The primary endpoint was mortality from any cause. Analyses were by intention to treat.

**Findings** Between 1994 and 1997, 4927 patients were enrolled. 1776 had recurrences and 1576 died. Survival was similar with high-dose and low-dose folinic acid (70.1% vs 71.0% at 3 years;  $p=0.43$ ), as were 3-year recurrence rates (36.0% vs 35.8%;  $p=0.94$ ). Survival was worse with levamisole than with placebo (69.4% vs 71.5% at 3 years;  $p=0.06$ ), and there were more recurrences with the active drug (37.0% vs 34.9% at 3 years;  $p=0.16$ ).

**Interpretation** The inclusion of levamisole in chemotherapy regimens for colorectal cancer does not delay recurrence or improve survival. Higher-dose folinic acid produced no extra benefit in these regimens over that from low-dose folinic acid. Trials of chemotherapy versus no chemotherapy will show whether these four treatments are equally effective or equally ineffective.

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## Introduction

Colorectal cancer is the second most common malignant disease in developed countries, with 700 000 new cases and 500 000 deaths worldwide each year.<sup>1</sup> The primary treatment, surgery, is possible in about 70% of patients, but about a half of those who undergo surgery subsequently develop incurable recurrent disease.

Cytotoxic chemotherapy after apparently complete resection can lower this high risk of recurrence. Such adjuvant chemotherapy commonly consists of treatment for 6 months or longer with fluorouracil-containing regimens, but there is uncertainty as to which regimens are most effective. Of the combinations tested, two of the most promising are fluorouracil plus levamisole and fluorouracil plus folinic acid. In an American Intergroup Study, there were 33% fewer deaths in the subgroup of patients with high-risk (Dukes' stage C) colon cancer who received fluorouracil and levamisole therapy for 1 year than in untreated controls.<sup>2</sup> UK and US consensus development conferences therefore recommended this combination as standard treatment for node-positive (stage C) colon cancer.<sup>3,4</sup> However, the contribution of levamisole, an anthelmintic immunomodulator, to the improved outcome was questioned.<sup>5</sup> Levamisole alone appeared ineffective,<sup>2,6</sup> the combination of fluorouracil and levamisole was no more effective than fluorouracil alone in advanced disease,<sup>7</sup> and the biological mechanism for the postulated synergy between these drugs was unclear.

Promising evidence was also reported from studies of adjuvant fluorouracil with its biomodulator, folinic acid.<sup>8–11</sup> Supplementation of the intracellular reduced folate pool by folinic acid prolongs the competitive inhibition of thymidylate synthase by forming a stable, ternary complex of the enzyme, reduced folate, and the cytotoxically active metabolite of fluorouracil, fluorodeoxyuracil monophosphate.<sup>12</sup> The benefits from adjuvant fluorouracil plus folinic acid were supported by this clear pharmacological rationale for potentiation of fluorouracil by folinic acid, and by definite evidence that folinic acid increased the activity of fluorouracil in advanced disease.<sup>13</sup>

The dose of folinic acid used in the adjuvant studies ranged from 20 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup>. The pharmacological mechanism suggests that the regimens with higher-dose folinic acid would be more effective than those with lower doses. Preclinical studies suggested a relation between dose of folinic acid and the intracellular concentrations of its active principle, methylene tetrahydrofolate. Moreover, higher doses of folinic acid had been associated with better inhibition of tumour growth in vitro and in mouse models of colorectal cancer. However, there was no empirical evidence that the high-dose regimens were more effective than the low-dose regimen, and the higher dose was more expensive.

\*Study organisation and collaborators given at end of paper

**Correspondence to:** QUASAR Study Office, CRC Clinical Trial Unit, Institute of Clinical Research, Medical School, Birmingham B15 2TT, UK

(e-mail: QUASAR@bham.ac.uk)

These encouraging results led to wider use of adjuvant fluorouracil-based chemotherapy for colorectal cancer. However, uncertainty remained about which patients should be offered chemotherapy and which regimen to use. A 1993 survey by the UK Coordinating Committee on Cancer Research of 500 UK clinicians who treated colorectal cancer found that about half offered at least some of their patients adjuvant chemotherapy—mainly young, high-risk patients (unpublished). About half of the clinicians who used chemotherapy reported using fluorouracil with folinic acid (at high or low dose) and most of the rest used fluorouracil with levamisole.

No previous randomised study has directly compared fluorouracil plus levamisole versus fluorouracil alone, or fluorouracil plus high-dose folinic acid versus fluorouracil plus low-dose folinic acid. Moreover, for realistically moderate survival differences between two such regimens (eg, 60% *vs* 65% 5-year survival) to be detected or refuted, such trials need to recruit not just several hundred, but several thousand patients.

The QUASAR (Quick And Simple And Reliable) trial was designed to provide large-scale randomised evidence on the true value of these different adjuvant chemotherapy regimens among different types of patient. There were two parts to QUASAR. One, which is still in progress and will be reported elsewhere, compared adjuvant with no adjuvant therapy. The second, reported here, compared various different fluorouracil-based adjuvant regimens to investigate whether levamisole and high-dose folinic acid, together or alone, confer additional benefit.

## Methods

### Patients

A patient was eligible if the responsible clinician judged that he or she had had a complete resection of colorectal cancer with no evidence of distant metastases and had no definite contraindications to any of the chemotherapy regimens. Patients with resection margins or peritoneal washings positive for malignant cells were not eligible. Definite contraindications to chemotherapy were specified not by the protocol but by the responsible clinician (and could involve both medical and other considerations). The patient's consent was sought before randomisation, and after a full written and oral explanation of the treatment options had been given. Ethical approval for the study was given by the local research ethics committee at each participating institute. Two categories of patient were included. The "certain" category consisted of patients whose clinicians were (for whatever reasons) reasonably certain that some form of adjuvant therapy was appropriate; the protocol required that all such patients were allocated one of the four study treatments. The "uncertain" category, which was smaller, consisted of patients who were randomly assigned adjuvant therapy or no adjuvant therapy because the clinician was uncertain whether any such treatment was appropriate. Those allocated active treatment were allocated one of the four study regimens and contribute data to this report (those allocated no active treatment do not).

### Design and procedures

In a two×two factorial design, patients were randomly assigned either high-dose or low-dose folinic acid and either levamisole or placebo (figure 1). The treatments were given for 6 months in combination with fluorouracil at the same fixed dose for all patients. Where possible, adjuvant treatment had to begin within 6 weeks of surgery. The levamisole/placebo randomisation closed in July, 1997, when supplies of levamisole ran out, so there are 64 fewer patients (4863) in the levamisole/placebo comparison than in the high-dose/low-dose folinic acid comparison.

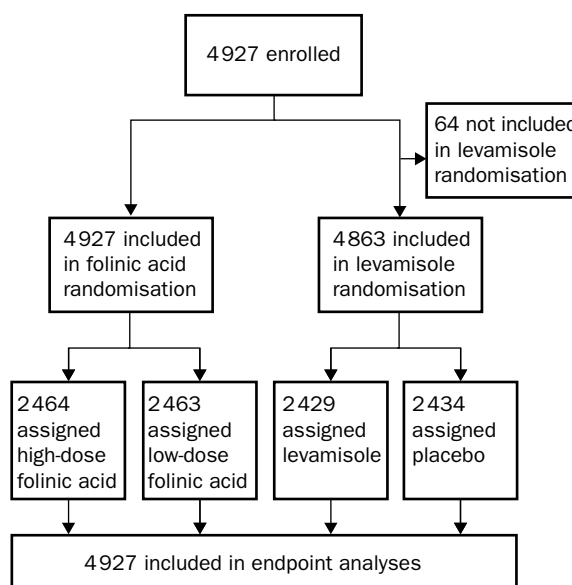


Figure 1: Trial profile

All chemotherapy patients received 30 doses of 370 mg/m<sup>2</sup> fluorouracil intravenously combined with either high-dose (175 mg intravenous fixed dose) or low-dose (25 mg intravenous fixed dose) L-folinic acid. 25 mg L-folinic acid, the active isomer, is equivalent to 50 mg DL-folinic acid.<sup>14,15</sup> The chemotherapy tested was a practicable outpatient regimen involving either six 5-day courses with 4-week intervals between the start of the courses or a once-weekly schedule for 30 weeks. The choice of schedule was decided by the clinician before randomisation. The 4-weekly schedule was recommended, but the once-weekly schedule was allowed if the 4-weekly schedule was impracticable—eg, because clinics were once a week. In the event of toxic effects between courses (on either schedule), the dose of fluorouracil for all subsequent courses was lowered, depending on the worst grade of toxic effects observed after the previous course.

Levamisole (or matching placebo) was given at 50 mg three times daily for 3 days repeated every 2 weeks for 12 courses. Chemotherapy and levamisole or placebo treatment started in the same week.

Trial drugs were supplied to each centre in treatment packs identified only by code numbers to ensure masking. To maintain double-blinding of folinic acid dose, syringes containing either 25 mg or 175 mg L-folinic acid in 20 mL normal saline were made up in the hospital pharmacy. Levamisole and placebo were provided in calendar packs containing capsules of identical appearance.

The use of radiotherapy for rectal cancers was left to the discretion of the responsible physician. The protocol recommended, however, that any radiotherapy should be given preoperatively, partly to avoid disruption of chemotherapy and partly because preoperative radiotherapy is at least as effective as postoperative radiotherapy in preventing local recurrence.<sup>16</sup> If postoperative radiotherapy was preferred, the chemotherapy regimen was slightly modified. Centres using the weekly fluorouracil plus folinic acid regimen could allow radiotherapy to coincide without any interruptions but with the fluorouracil dose decreased to 300 mg/m<sup>2</sup> during the period of radiotherapy. Centres using the 4-weekly schedule substituted one 5-day course of chemotherapy with a 5-week course of once-weekly chemotherapy during radiotherapy, again at 300 mg/m<sup>2</sup>, with a treatment-free interval of 4 weeks before the remaining 5-day courses of chemotherapy were given. For older or frail patients, for whom there were concerns about unacceptable toxic effects if chemotherapy and radiotherapy were given simultaneously, the protocol allowed suspension of chemotherapy during the period of radiotherapy and resumption 4 weeks after completion of radiotherapy. The levamisole regimen was unaffected by any radiotherapy.

To facilitate large-scale recruitment, QUASAR imposed the smallest possible extra workload on participating clinicians. Randomisation was by a short telephone call to the Oxford Clinical Trial Service Unit. The relevant characteristics of the patient were recorded during the phone call, so no entry form had to be completed. A minimised randomisation procedure was used, thereby ensuring that the trial treatments were evenly balanced with respect to age-group, site of cancer, stage, portal-vein infusion or not, preoperative radiotherapy or not, planned postoperative radiotherapy or not, chemotherapy schedule (weekly or not), and indication (certain or uncertain). Treatments were also partly balanced within participating centres through the QUASAR treatment cases. Apart from the trial treatments, all other management (eg, antiemetics, antibiotics) was entirely at the discretion of the local doctors. Patients were managed in whatever way seemed best for them, with the protocol imposing no special treatments or investigations, no delay of discharge, and no extra follow-up visits over the usual practice at each centre.

Collaborators were required to notify the trial office by telephone of any serious unexpected adverse experiences believed to be caused by chemotherapy. Apart from such notification, there was just one annual follow-up form, requesting brief details of serious toxic effects, recurrence, and death. This information was supplemented by the use of national mortality records to help ensure the completeness of long-term follow-up. Investigators were asked to provide extra details on the cause of death for patients who died without recorded recurrence. Also, pharmacists were supplied with a QUASAR pad to record the treatment pack used, the dates of drug administration, and the fluorouracil dose and schedule. Copies of these pads were obtained once patients had completed chemotherapy. Data on health economics, compliance, detailed treatment toxicity, and quality of life were assessed for about 600 patients in a substudy that will be reported elsewhere.

	Folinic-acid dose comparison		Levamisole comparison	
	High-dose (n=2464)	Low-dose (n=2463)	Levamisole (n=2429)	Placebo (n=2434)
<b>Age (years)</b>				
<50	375	376	369	372
50-59	647	652	638	640
60-69	968	964	953	953
≥70	474	471	469	469
Median	62	62	62	62
IQR	54-68	54-68	54-68	54-68
Range	15-86	22-86	20-86	15-86
<b>Sex</b>				
Male	1457	1451	1437	1434
Female	1007	1012	992	1000
<b>Site of cancer</b>				
Colon	1680	1678	1651	1659
Rectum	703	707	700	696
Both	81	78	78	79
<b>Dukes' stage</b>				
A	5	6	2	9
B	682	681	664	660
C	1777	1776	1763	1765
<b>Portal-vein infusion</b>				
No	2451	2455	2418	2424
Yes	13	8	11	10
<b>Preoperative radiotherapy</b>				
No	2368	2365	2335	2337
Yes	96	98	94	97
<b>Planned postoperative radiotherapy</b>				
No	2057	2058	2024	2030
Yes	407	405	405	404
<b>Randomisation option</b>				
Clear indication	2160	2160	2146	2150
Uncertain indication	304	303	283	284
<b>Chemotherapy schedule</b>				
Every week	1188	1182	1169	1174
Every 4 weeks	1276	1281	1260	1260

Table 1: Characteristics of patients at baseline

### Statistical analyses

QUASAR aimed to recruit 5000 patients in total, which would give a chance of more than 80% that the study could detect a 5% difference in 5-year survival (eg, 60% *vs* 65%) from addition of levamisole to fluorouracil plus folinic acid, or from use of high-dose rather than low-dose folinic acid. The main endpoint for treatment evaluation was all-cause mortality. Subsidiary endpoints were death from colorectal cancer and recurrence. Both the subsidiary analyses ignored deaths due to other causes without recorded recurrence. All treatment comparisons were by intention to treat and used standard log-rank methods. Tests for heterogeneity of treatment effects within subgroups also used standard log-rank methods.<sup>17</sup>

During the recruitment period, interim analyses of mortality (and of any other information on major endpoints that was available) were supplied, in strict confidence, to an independent data-monitoring committee, along with any other analyses that the committee requested. The committee's remit was to notify the chairman of the trial's steering committee if the randomised comparisons in QUASAR provided proof beyond reasonable doubt that for all, or for some, types of patient one particular treatment was clearly indicated or clearly contraindicated in terms of a net difference in long-term survival, and evidence that might reasonably be expected to influence the management of patients by many clinicians who are already aware of the other main trial results. The steering committee would then decide whether to modify intake to the study. Unless this happened, however, the steering committee, the collaborators, and all the central administrative staff (except the statisticians who supplied the confidential analyses) remained ignorant of the interim results.

## Results

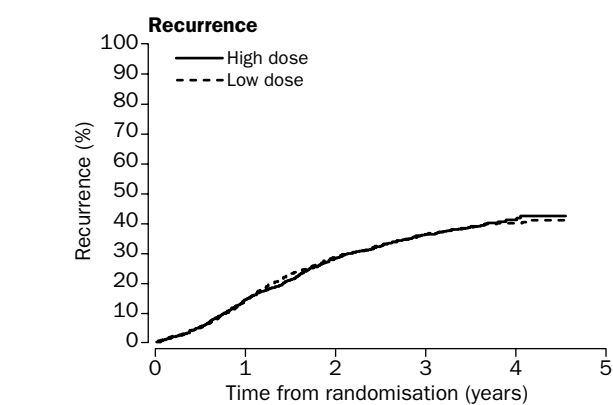
### Characteristics of patients

The trial opened in May, 1994. Randomisation between the high-dose and low-dose folinic acid regimens closed in October, 1997, by which time 4927 patients had been randomised by 320 doctors from 134 centres in five countries (figure 1). Because randomisation involved minimisation, the study groups were well balanced in terms of baseline characteristics (table 1). The median age was 62, 59% of the participants were male, and 68% had colon cancer. The disease was of Dukes' stage C (node-positive) in 72%, stage B in 28%, and stage A in 0.2%. 4% (12% of rectal cancer patients) had received preoperative radiotherapy; 16% (42% of rectal cancers) were scheduled for postoperative radiotherapy. Chemotherapy was scheduled to be every 4 weeks for 52% of patients and once a week for 48%.

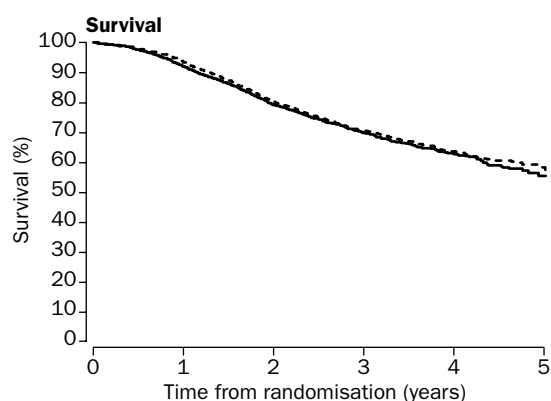
The main assessment of folinic acid doses compared the 2464 patients who were assigned high-dose folinic acid with the 2463 who were assigned low-dose folinic acid, irrespective of whether they were assigned levamisole (figure 1). The main assessment of levamisole compared the 2429 patients who were assigned active levamisole with the 2434 who were assigned placebo, irrespective of their dose of folinic acid; the 64 patients who did not enter the levamisole randomisation are not included in this comparison.

### Follow-up

95% of patients were entered from the UK. Of these, 93% were flagged with the national death registry, and copies of death certificates for all flagged participants who died were sent to the trial office, usually within 3 months. Flagged patients from England and Wales are assumed to be alive as of April 30, 1999, and those from Scotland as of Jan 31, 1999, unless notified otherwise. In addition, a



Number still at risk						
High dose	2464	2048	1428	602	93	1
Low dose	2463	2064	1410	585	90	



Number still at risk						
High dose	2464	2231	1867	1163	428	33
Low dose	2463	2266	1885	1169	398	26

Figure 2: Risk of recurrence and survival for 4927 patients randomly assigned high-dose or low-dose folinic acid

postal follow-up of the status of all patients was undertaken in January, 1999. Replies to this follow-up have been received for 93% of patients. For analyses of recurrence, and for survival analyses for patients who have not been successfully flagged, analyses were censored at January, 1999, if a follow-up reply had been received, or at last follow-up otherwise. The median follow-up of the surviving patients is 3 years (range 1.5–5.0).

#### High-dose versus low-dose folinic acid

There was no difference in recurrence rate between the folinic acid groups (figure 2); there were precisely the same number of recurrences in the high-dose and low-

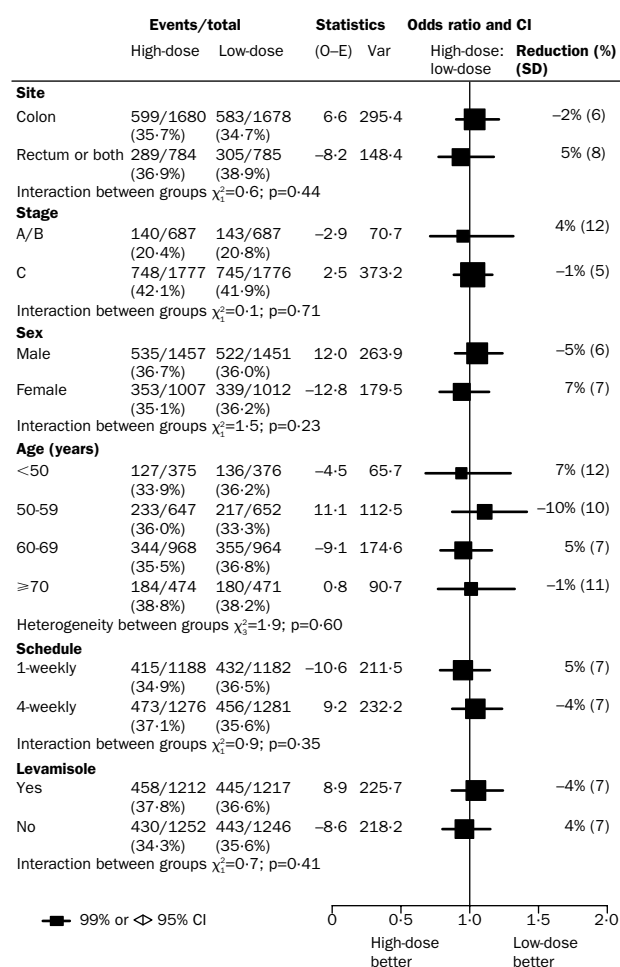


Figure 3: Risk of recurrence according to assignment to high-dose or low-dose folinic acid, by various characteristics of patients, tumours, and treatments

O=observed; E=expected; Var=variance.

dose groups (888/2464 vs 888/2463). The 3-year risk of recurrence was 36.0% with high-dose folinic acid and 35.8% with low-dose folinic acid (difference 0.2% [SD 1.6]). The odds ratio of recurrence in the high-dose versus the low-dose group was 1.00 (95% CI 0.91–1.09;  $p=0.94$ ).

There was little difference in survival between the two groups, with slightly more deaths in the high-dose group (801 vs 775). 3-year survival was 70.1% with high-dose and 71.0% with low-dose folinic acid (difference 0.9% [SD 1.3]). The odds ratio of death in the high-dose group compared with the low-dose group was 1.04 (0.94–1.15;  $p=0.43$ ).

	Folinic-acid dose comparison			Levamisole comparison		
	High-dose	Low-dose	Odds ratio (95% CI)	Levamisole	Placebo	Odds ratio (95% CI)
Diarrhoea	362	338	1.08 (0.92–1.27)	337	356	0.93 (0.80–1.10)
Stomatitis	216	158	1.40* (1.13–1.74)	181	191	0.95 (0.77–1.17)
Vomiting/nausea	169	150	1.14 (0.91–1.43)	173	143	1.23 (0.98–1.55)
Any haematological	111	116	0.95 (0.73–1.25)	109	117	0.93 (0.71–1.22)
Dermatological	95	79	1.21 (0.89–1.64)	110	63	1.79† (1.30–2.45)
Cardiovascular	42	37	1.14 (0.73–1.78)	39	40	0.98 (0.63–1.52)
Neurological	22	22	1.00 (0.55–1.81)	25	19	1.32 (0.73–2.41)
Other or unspecified	327	285	1.17 (0.99–1.39)	325	283	1.17 (0.99–1.39)
Any fluorouracil dose reduction	33%	30%	1.14 (0.99–1.30)	32%	31%	1.06 (0.92–1.21)
Completion of chemotherapy	69%	70%	0.99 (0.93–1.06)	68%	70%	0.96 (0.90–1.03)
Completion of levamisole	67%	68%	0.95 (0.83–1.09)	65%	70%	0.77* (0.68–0.89)

$p>0.05$  for all comparisons except: \* $p=0.002$ ; † $p<0.0001$ .

Table 2: Numbers of toxic events reported by treatment

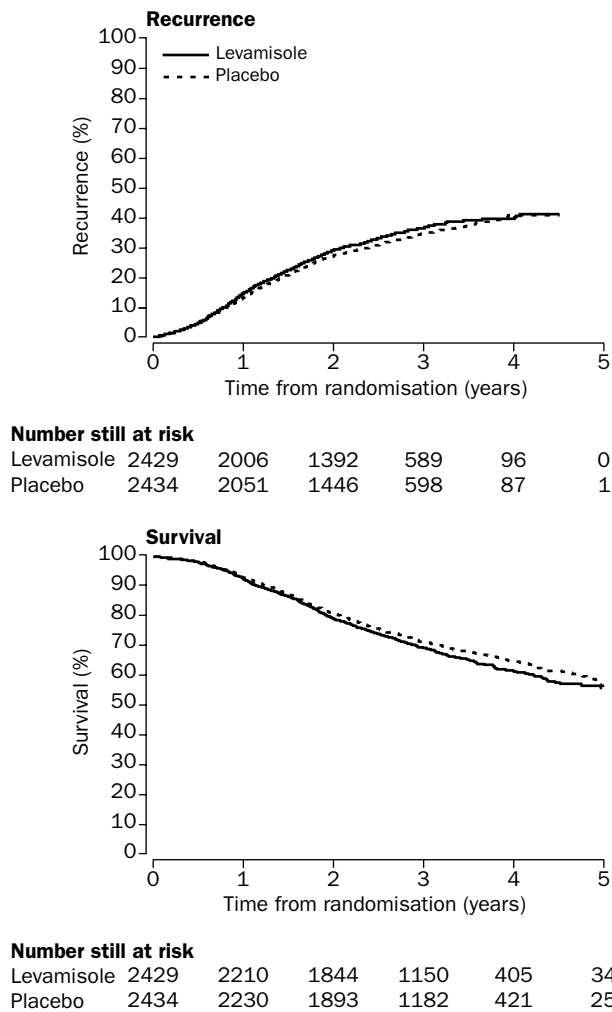


Figure 4: Risk of recurrence and survival for 4863 patients randomly assigned levamisole or placebo

Figure 3 shows the odds of recurrence for high-dose versus low-dose folinic acid in various subgroups of patients or treatment. In none of these subgroups, however, was there good evidence that high-dose folinic acid was better or worse than low-dose folinic acid. None of the subgroup differences was significant.

Although toxicity data were not systematically sought for all patients, comparisons between groups are unlikely to be biased in relation to treatment allocation because the study was double-blind. The only significant difference in toxic effects seen between the high-dose and low-dose folinic acid groups was in the number of patients reporting stomatitis (table 2). However, this apparent excess with high-dose folinic acid could be a chance finding given the many types of toxic effects investigated. Information on compliance was available for 81% of patients on 3997 pharmacy record cards. The proportions of patients completing the 6 months of chemotherapy and the proportions taking the full course of levamisole or placebo capsules were similar in the high-dose and low-dose folinic acid groups.

*Levamisole versus placebo*

There were more recurrences among the patients assigned levamisole than among those assigned placebo (903/2429 vs 862/2434 recurrences; figure 4). The risk of recurrence at 3 years was 37.0% with levamisole and 34.9% with

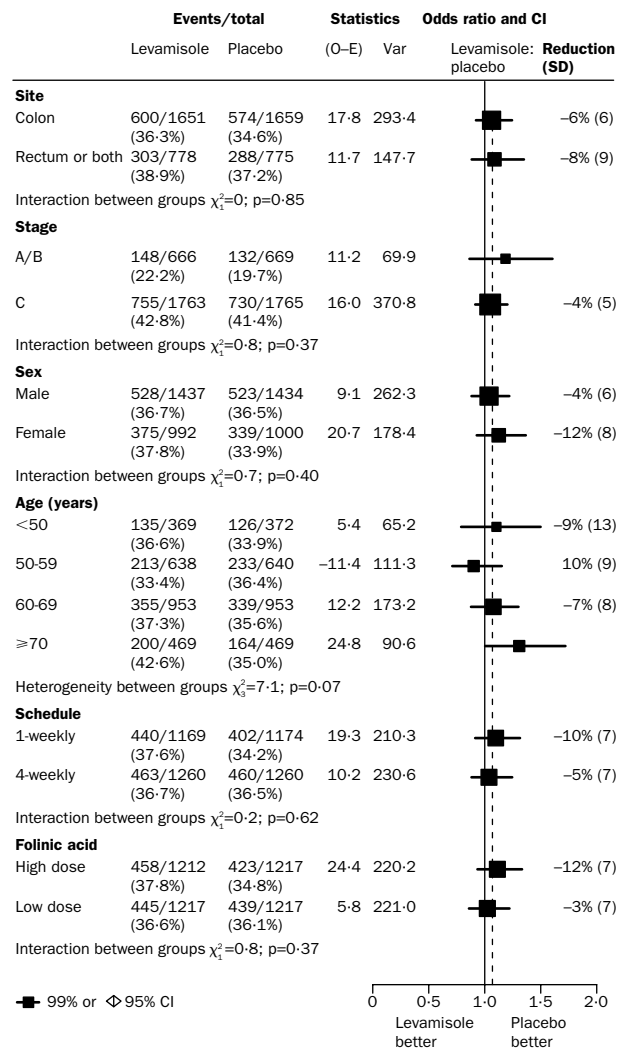


Figure 5: Risk of recurrence according to assignment to levamisole or placebo, by various characteristics of patients, tumours, and treatments

Abbreviations as for figure 3.

placebo (difference 2.1% [SD 1.6]). The odds ratio for recurrence with levamisole compared with placebo was 1.07 (95% CI 0.97-1.17; p=0.16).

Similarly, no survival benefit from levamisole was apparent, with more deaths among patients assigned levamisole than among those assigned placebo (815 vs 755). 3-year survival was 69.4% with levamisole and 71.5% with placebo (difference 2.1% [SD 1.4]). The odds ratio for death with levamisole compared with placebo was 1.10 (1.00-1.22; p=0.06).

The various subgroup analyses (figure 5) gave no indication that any category of patient would benefit from levamisole. In particular, no selective benefit was apparent in colon cancer or in stage C cancer, subgroups reported to benefit in a previous study.<sup>2</sup> Among patients over age 70, the risk of recurrence was significantly higher in those allocated levamisole than in those allocated placebo. However, this heterogeneity of treatment effect within age-groups was not significant (p=0.07) and could well be a chance finding, given the number of subgroups investigated.

There was a highly significant excess of dermatological toxic effects with levamisole (table 2) but no other significant differences in toxic effects. Vomiting or nausea

Study	Total enrolled	Eligible (efficacy)	Doses (mg/m <sup>2</sup> )			Tumour response (%)		Median survival (weeks)	
			Fluorouracil	High-dose folinic acid	Low-dose folinic acid	High-dose	Low-dose	High-dose	Low-dose
PALL-1 1996 <sup>18</sup>	325	291	500	500	20	22	18	55	54
Petrelli 1989 <sup>19</sup>	343	328	600	500	25	30	19	55	45
Ychou 1998 <sup>20</sup>	83	73	400	200	20	8	16	46	49

Table 3: Summary of trials in advanced colorectal cancer that compared high-dose and low-dose folinic acid

and “other” toxic effects were reported about 20% more frequently with levamisole than with placebo but these differences did not reach significance, perhaps because of small numbers of events. Haematological toxic effects, diarrhoea, and stomatitis occurred at the same frequency in the two groups. A significantly smaller proportion of patients completed the levamisole course than completed the placebo course (table 2). Similarly, a smaller proportion of the levamisole group than of the placebo group completed the fluorouracil and folinic acid chemotherapy, but this difference was not significant.

#### Serious adverse events

Serious, unexpected adverse events were rare; almost all the toxic effects seen were those expected with these chemotherapy regimens. To check the completeness of reporting of treatment-related deaths, all deaths without recorded recurrence that occurred within 9 months of randomisation were reviewed and extra information was sought on their causes. Only four were believed to be related to the toxicity of chemotherapy. This 0.1% treatment-related mortality seen in QUASAR shows that the regimens tested are safe, even in a large multicentre trial.

#### Discussion

Because the QUASAR study is large, its overall findings provide reliable evidence that there is little or no difference in clinical efficacy between high-dose and low-dose folinic acid, or between levamisole and placebo. Three small studies in advanced disease have compared response and toxic effects for high-dose and low-dose folinic acid regimens, and in aggregate they found no obvious differences (table 3).<sup>18–20</sup> Studies that reported similar efficacy but less toxicity with high-dose folinic acid used a lower dose of fluorouracil with high-dose folinic acid than with low-dose folinic acid, which may well account for the lower toxicity. There is, therefore, no worthwhile benefit from use of high-dose folinic acid to potentiate fluorouracil; if a combination of fluorouracil and folinic acid is to be used, the cheaper low-dose regimen (25 mg L-folinic acid or 50 mg DL-isomer) should be used in routine clinical practice.

This conclusion is consistent with re-examination of the cellular pharmacology of folinic acid, which suggests that plasma concentrations over 1 µmol/L of the active (reduced) metabolite of folate may adequately expand intracellular folate pools. Plasma concentrations of reduced folate are maintained above 1 µmol/L for more than 1 h after an intravenous bolus of 50 mg DL-folinic acid; this finding supports the concept that low-dose folinic acid is sufficient.

If this conclusion is correct, several commonly used chemotherapy regimens that include high-dose folinic acid are doing so unnecessarily. For example, the Machover regimen, which was shown to be effective in the International Multicentre Pooled Analysis of Colorectal Cancer Trials studies,<sup>9</sup> is identical to the 4-weekly high-

dose folinic acid regimen tested in QUASAR. We can therefore conclude that equivalent results would have been achieved with 20 mg/m<sup>2</sup> instead of 200 mg/m<sup>2</sup> DL-folinic acid. There was no selective benefit of high-dose folinic acid when used in the once-weekly schedule of fluorouracil and folinic acid in QUASAR, so high-dose folinic acid (500 mg/m<sup>2</sup>) is probably also unnecessary in the once-weekly Roswell Park regimen, which was used in the National Surgical Adjuvant Breast and Bowel Project C-03 study.<sup>11</sup> Finally, treatments based on the de Gramont regimen, with or without extra drugs, are widely used in advanced disease and use high-dose bolus folinic acid with fluorouracil before a 2-day continuous infusion of fluorouracil, but there is no good reason to believe that high-dose folinic acid is important in this context. Use of low-dose folinic acid, at much less expense, in these regimens should be equally effective.

Our findings effectively rule out any worthwhile reduction in the risk of death with levamisole. Results of other studies reinforce the QUASAR findings. The National Surgical Adjuvant Breast and Bowel Project C-04 and Intergroup 0089 studies both reported equivalent survival with fluorouracil plus folinic acid and with fluorouracil plus folinic acid plus levamisole, and better survival with fluorouracil plus folinic acid than with fluorouracil plus levamisole.<sup>21,22</sup> Another study directly tested the value of levamisole as used in the Moertel regimen by comparing 1 year of fluorouracil alone with 1 year of fluorouracil plus levamisole, and again found no benefit from levamisole.<sup>23</sup> That study was too small to rule out a moderate survival improvement, but it did not support the biologically unlikely hypothesis that levamisole adds to the effectiveness of fluorouracil alone but adds nothing to fluorouracil plus folinic acid. Levamisole alone seems ineffective in colorectal cancer,<sup>6</sup> and no direct randomised assessment of levamisole added to various fluorouracil regimens has shown benefit.

If levamisole adds nothing to fluorouracil, as now seems clear, what explains the large (33% reduction in death rate) benefit seen in the Intergroup 0035 study<sup>2</sup> of fluorouracil plus levamisole? This reported benefit is a little inflated by emphasis on the stage C subgroup. The overall survival benefit in that study was a 25% reduction in mortality, which was somewhat smaller than that reported for stage C patients because the parallel comparison among stage B patients found less benefit.<sup>5</sup> Nevertheless, fluorouracil plus levamisole does seem effective, because the 0035 study results are reinforced by the report of a significant reduction in mortality with fluorouracil plus levamisole compared with a no-chemotherapy group in a Dutch “confirmatory” study.<sup>24</sup> Given the QUASAR results, however, the likely explanation for these findings is the high dose intensity and duration of exposure to fluorouracil and not the inclusion of levamisole.<sup>25</sup> The Moertel regimen without levamisole would, therefore, probably be equally effective, and a little less toxic. Even so, fluorouracil plus folinic acid seems preferable to fluorouracil plus levamisole

because of the shorter treatment period, and because direct randomised comparisons suggest that fluorouracil plus folinic acid is at least as effective as fluorouracil plus levamisole.<sup>21,22,26</sup>

Another important message from QUASAR is that large-scale recruitment to cancer trials can be achieved by simplifying trial procedures and, thereby reducing the burden on participating clinicians. In particular, few outcome data were collected on each patient, and no extra investigations or follow-up visits were required. Reliability is not compromised by this approach, particularly because the study was double blinded. Data on the main endpoint, survival, were collected in an unbiased way through the Office of National Statistics. This central flagging of UK QUASAR patients was supplemented by annual follow-up of all surviving patients. Cross-checking between these independent data sources confirmed the completeness and high reliability of the information provided. Cross-checking between pharmacy record cards and information collected in the detailed toxicity substudy also found high concordance. Baseline data, recorded at randomisation, were not checked systematically against source data; nor were dates of recurrence, except to resolve inconsistencies. However, the probably small numbers of misclassifications of age or stage, or imprecisions in dates of recurrence, would have negligible effect on statistical power, and would not materially change the study findings.<sup>27</sup> Thus, the simplification of QUASAR trial procedures does not reduce the reliability of the study findings. Instead, the reduction of random error through the much larger numbers of patients entered increased the reliability of the findings.<sup>28</sup>

The lack of any apparent differences in efficacy among the four chemotherapy regimens tested raises the question of whether they were all equally effective or all equally ineffective. The latter seems unlikely; although the absolute survival differences are moderate, the controlled trials of fluorouracil plus folinic acid versus no chemotherapy collectively show a highly significant benefit.<sup>29</sup>

However, there remains uncertainty about which patients derive sufficient benefit from chemotherapy to justify the toxicity, inconvenience, and cost, and how long any survival benefits from chemotherapy persist. In particular, a worthwhile benefit from fluorouracil plus folinic acid for patients with disease of Dukes' stage B is not yet firmly established<sup>30</sup> and there is no direct confirmation of benefit for patients with rectal cancer<sup>23</sup> to justify their widespread treatment. The continuing QUASAR-1 study will help resolve these uncertainties about the appropriate use of chemotherapy.

#### QUASAR study organisation

*Writing committee*—RG Gray (Clinical Trials Unit, University of Birmingham); DJ Kerr, CC McConkey (CRC Institute of Cancer Studies, University of Birmingham); NS Williams (Royal London Hospital, London); RK Hills (CRC Institute of Cancer Studies, University of Birmingham).

*Data-monitoring committee*—DG Altman (Imperial Cancer Research Fund, London); R Collins (ICRF/MRC Clinical Trial Service Unit, Oxford); R Souhami (chair; University College Hospitals, London)

*Steering committee*—J Cassidy (Aberdeen Royal Infirmary); J Dunn (CRC Trials Unit, University of Birmingham); P Finan (Leeds General Infirmary); RGT Glynn-Jones (Mount Vernon Hospital, Northwood); RG Gray, RD James (Maidstone Hospital); P Johnston (Queen's University, Belfast); DJ Kerr (clinical coordinator); J Ledermann (University College Hospitals, London); C Marks (Royal Surrey County Hospital, Guildford); T Maughan (Velindre Hospital, Cardiff); CS McArdle (Royal Infirmary of Edinburgh); N Mortensen (Oxford Radcliffe Hospitals); J Mossman (BACUP, London); C Normand (London School of Hygiene and Tropical Medicine); JMA Northover

(St Mark's Hospital, London); P Price (Hammersmith Hospital, London); P Quirke (University of Leeds); D Sebag-Montefiore, M Seymour (Cookridge Hospital, Leeds); D Smith (Clatterbridge Hospital, Wirral); D Spiegelhalter (MRC Biostatistics Unit, Cambridge); A Stanley (City Hospital, Birmingham); P Twentyman (UKCCCR, London); M Watson (Royal Marsden Hospital, London); NS Williams (chair).

*Administration*—N Armstrong, M Collingwood, A Donald, C Harwood, S Knight, C Marsden, G Mead, J Notman, A Peto, A Radley (ICRF/MRC Clinical Trial Service Unit, Oxford); J Barnwell, D Moffitt, E Perry, J Smith, L Ward (Trials Unit, University of Birmingham).

*Quality of life/health economics substudies*—C Normand, W Stevens (London School of Hygiene and Tropical Medicine); M Watson, J Davidson (Royal Marsden Hospital, London).

*Collaborators* (\*Local clinical coordinator)—Aberdeen Royal Infirmary (AK Ah-See, V Bain, NB Binnie, D Bissett, J Cassidy\*, AIG Davidson, O Eremin, AW Hutcheon, L Johnstone, RA Keenan, P King, NM Koruth, ZH Krukowski, SS Miller, TJ O'Kelly, AJ Park, KGM Park); Addenbrooke's, Cambridge (P De Takats, J Hirst, R Miller, J Pratt, TK Wheeler, CBJH Wilson\*); Adelaide and Meath, Dublin (J Armstrong, WH Beesley, J Geoghegan, FBV Keane\*, S Smith, WA Tanner\*, H Wilson); Aintree, Liverpool (CF Mackie); Airedale General (SM Crawford, EP Dewar, J Hale, CR Kapadia\*, WAF McAdam, T Wright); Alexandra, Redditch (L Barnish, R Brown, S Cook, RJ Grieve, C Irwin\*, F Nash, R Tudor); Alexandra House, Guernsey (P Riley\*); Arrowe Park, Liverpool (KF Edwardson, CA Makin, S Sagar); Ashford, Kent (WNW Baker); Ayr (A Bryden, JA Elliott, JC Ferguson\*, J McDermid, C Wilson); Barnet General (IC Mitchell); Barnsley District (JJ Bannister, RT Waddington); Basildon (I Linehan); Bassetlaw District General (ID Crate); Bate, Reading (RG Faber); Beaumont, Dublin (JM Deasy, B Lane, P Molloy, H Osbourne, HP Redmond\*, A Staunton); Birmingham Heartlands/Solihull (G Barsoum, RA Cobb, I Fernando, M Gannon, Y Hanson, N James, M Leyland\*, D Richardson, C Russell, GS Sokhi); Bishop Auckland General (AN Branson, B Kell, A Milligan, JG Stephen\*); Blackburn Royal Infirmary (DA Evans); Bolton Royal Infirmary (GH Ferguson, JH Hobbiss); Bradford Royal Infirmary (RM Antrum, JR Ausobsky, C Bradley\*, H Flint, J King, D Parker, JJ Price); Bridlington and District (J Macfie\*, A Wood, S Woodcock); Bristol Royal Infirmary (M Ball, VL Barley, AE Brewster, J Bullimore, P Durley, HJ Espiner, S Falk\*, JD Graham, R Harris, RE Hawkins, K Hopkins, O McGrath, C Price, MG Thomas, EC Whipp); Broomfield, Chelmsford; (M Harvey\*, AHM Ross, P Sauven); Burnley General (HR Gattamaneni); Castle Hill, Hull (GS Duthie, PWR Lee, JRT Monson, KR Wedgwood); Central Middlesex (MM Henry, N Menzies-Gow); Charing Cross (RC Coombes, PJ Gomes\*, IWF Hanham, S Haynes, CP Lowdell, ES Newlands, S Patel, RH Phillips, BM Southcott, RJ Springall); Cheltenham General (A Ashton, K Benstead\*, R Counsell, S Elyan, AJ Goodman, S Haynes, I Ingledew, HJ Owen, KR Poskitt, R Wallis); Chesterfield Royal (D Bardsley, WG Lambert, JM Simms); Chorley and District (M Mughal\*); Christchurch, New Zealand (CH Atkinson, P Barrett, BM Fitzharris, B Robinson\*, L Skelton); Christie, Manchester (H Anderson, A Burgess, PA Burt, RA Cowan, L Howard, RD James\*, E Levine, J Logue, ST O'Dwyer, JH Scarffe, J So, PN Wake, PM Wilkinson); Christo Road, Waratah, Australia (S Cox); City, Nottingham (EM Bessell, J Carmichael, S Chan, S Gardner, SA Morgan, M Robinson, MPJW Sokal, K Stainer, JL Wilkins, CB Williams, PJ Wolf\*); City, Birmingham (IA Donovan, M Fisher, J Glaholm, DJ Kerr\*, MJR Lee, ML Obeid, D Peake, D Rea, SH Silverman, D Spooner, R Spychal, A Stanley, RL Wolverson, A Young); Clatterbridge, Liverpool (DA Berstock, C Bull, PI Clark, RD Errington, K Hannighan, J Koundakjian, E Marshall, S Myint, SM O'Reilly, S Sagar, A Slater, D Smith\*); Clinical Trial Service Unit, Oxford (R Peto, D Sinclair); Colchester General (G Edgett, A May, D Menzies, RW Motson, A Zaborszky); Cookridge, Leeds (HJ Close, C Coyle, A Jones, F Richards, D Sebag-Montefiore, M Seymour\*); Countess of Chester (P Edwards, JF Kane); Crawley (JC Bull, ERTC Owen, C Topham); Cumberland Infirmary (WJ Glendinning, JJ Nicoll\*, JG Palmer, A Wright); Darlington Memorial (AE Clason, M Whittaker\*); Derby City (JR Reynolds); Derbyshire Royal Infirmary (E Bedford, M Gudgeon, RI Hall, S Miller, JR Nash, GD Thomas\*); Derriford, Plymouth (K Bolter, AJM Brodribb, C Brown, F Daniel\*, P Gray, E Pace, JFL Shaw, C Teasdale, RM Watkins, DW Wilkins); Doncaster Royal Infirmary (GB Coombes, G Jacob, WSJ Mair); Dorset County (P Ashcroft, DD Meikle); Dr Gray's, Elgin (D Bissett\*, I Gunn, R McIntyre, JDB Miller, J Sim); Dryburn, Durham (AIM Cook); Dunedin, New Zealand (D Perez\*); East Surrey, Reigate (A Bates, F Broad, A Folkes\*, JE Hale, RG Lightwood); Eastbourne District General (PL Brooks, G Evans, PH Rowe, BJ Stoodley); Eastern General, Edinburgh (RJ Aitken); Edgware General (RA Harrison); Essex County (C Backhouse, D Gamble, J Kent, S Moat, P Murray, WR Pratt\*, B Sizer, S Tahir); Falkirk Royal Infirmary (JAE McDonald); Freeman, Newcastle (PJ Hainsworth); Frenchay, Bristol (CP Armstrong, AR Baker, RE May); Friarage, Northallerton (DC Ward); Frimley Park, Frimley (C Keith, R Laing\*, S Pillar, KRP Rutter); Furness General

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Velindre (M Adams, AE Brewster, NG Burnet, T Crosby, C Gaffney, S Gollins, I Kirby, TS Maughan\*, D Mort, C Parsons, ICM Paterson, S Rivers); Victoria, Blackpool (C Boardman, B Bradely, M Flannagan, ME Lambert, S Ravi, S Walker); Victoria, Kirkcaldy (A Boyd, C Mclean); Victoria Infirmary, Glasgow (GR Gray\*, IR Pickford); Walsgrave, Coventry (J Chapman, IA Fraser, RJ Grieve\*, D Halliman, C Irwin, DA Jones, SH Kashi, FT Lam, S Marsh, GAG Mogg, RW Parker, PN Roberts, AD Stockdale); Warrington District General (MCA Brett, BA Taylor); Watford General (J Meyrick-Thomas); West Dorset (M Al-Hilali\*, P Giles, P Jeffery, RJ Osborne); West Middlesex University (PM Dawson); West Suffolk (D Lawrence); Western General, Edinburgh (D Jodrell\*, C McLean,



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