Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

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Summary

Background The aim of the QUASAR trial was to determine the size and duration of any survival benefit from adjuvant chemotherapy for patients with colorectal cancer at low risk of recurrence, for whom the indication for such treatment is unclear.

Methods After apparently curative resections of colon or rectal cancer, 3239 patients (2963 [91%] with stage II [node negative] disease, 2291 [71%] with colon cancer, median age 63 [IQR 56–68] years) enrolled between May, 1994, and December, 2003, from 150 centres in 19 countries were randomly assigned to receive chemotherapy with fluorouracil and folinic acid (n=1622) or to observation (with chemotherapy considered on recurrence; n=1617). Chemotherapy was delivered as six 5-day courses every 4 weeks or as 30 once-weekly courses of intravenous fluorouracil (370 mg/m²) with high-dose (175 mg) L-folinic acid or low-dose (25 mg) L-folinic acid. Until 1997, levamisole (12 courses of 450 mg over 3 days repeated every 2 weeks) or placebo was added. After 1997, patients who were assigned to receive chemotherapy were given fluorouracil and low-dose folinic acid only. The primary outcome was all-cause mortality. Analyses were done by intention to treat. This trial is registered with the International Clinical Trial Registry, number ISRCTN82375386.

Findings At the time of analysis, 61 (3·8%) patients in the chemotherapy group and 50 (3·1%) in the observation group had missing follow-up. After a median follow-up of 5·5 (range 0–10·6) years, there were 311 deaths in the chemotherapy group and 370 in the observation group; the relative risk of death from any cause with chemotherapy versus observation alone was 0·82 (95% CI 0·70–0·95; p=0·008). There were 293 recurrences in the chemotherapy group and 359 in the observation group; the relative risk of recurrence with chemotherapy versus observation alone was 0·78 (0·67–0·91; p=0·001). Treatment efficacy did not differ significantly by tumour site, stage, sex, age, or chemotherapy schedule. Eight (0·5%) patients in the chemotherapy group and four (0·25%) in the observation group died from non-colorectal cancer causes within 30 weeks of randomisation; only one of these deaths was deemed to be possibly chemotherapy related.

Interpretation Chemotherapy with fluorouracil and folinic acid could improve survival of patients with stage II colorectal cancer, although the absolute improvements are small: assuming 5-year mortality without chemotherapy is 20%, the relative risk of death seen here translates into an absolute improvement in survival of 3·6% (95% CI 1·0–6·0).

Introduction

Colorectal cancer is the second most common malignant disease in developed countries, with 1 million new cases and 500 000 deaths worldwide every year.[1] Cytotoxic chemotherapy, after apparently complete resection, can lower the risk of recurrence, but there has been debate over which patients benefit from such adjuvant treatment and which drug regimens are most effective. A 1-year course of fluorouracil plus levamisole[2,3] was widely recommended as standard treatment for stage III (node positive) colon cancer in the early 1990s.[4,5] However, subsequent evidence has established that a 6-month regimen of fluorouracil coupled with folinic acid[6–9] is at least as effective,[10–12] and that adding levamisole to fluorouracil regimens does not improve outcome.[10,13] The benefits from adjuvant fluorouracil and folinic acid are supported by a clear pharmacological rationale[14] and by definite evidence that folinic acid enhances the activity of fluorouracil in advanced disease.[15]

Chemotherapy with fluorouracil and folinic acid has, therefore, become widely used for stage III (node positive) colon cancer. However, there remains uncertainty whether stage II (node negative) patients derive sufficient benefit from adjuvant chemotherapy to justify the toxicity, costs, and inconvenience of treatment.[16] Furthermore, although the effect of adjuvant chemotherapy is assumed to be similar in rectal and colon cancer, there is little direct randomised evidence to support this. Giving fluorouracil concurrently with radiotherapy does seem to improve survival over radiotherapy alone,[17] but this could be due to synergy between radiotherapy and fluorouracil. Most previous trials of fluorouracil and folinic acid have included only patients with colon cancer, and a Dutch trial of fluorouracil and levamisole showed benefit in colon but not rectal cancer.[3] Consequently, there has been doubt among many clinicians whether patients with rectal cancer—whether node positive or negative—benefit from adjuvant chemotherapy. The QUASAR (QUick And Simple And Reliable) trial was designed to provide large-scale randomised evidence on the value of adjuvant chemotherapy with fluorouracil and folinic

acid in both colon and rectal cancer and, in particular, in stage II disease.

Methods

Patients

Patients were eligible if they were thought to have had a complete resection of colon or rectal cancer with no evidence of distant metastases, and if they had no definite contraindications to chemotherapy. No prior chemotherapy was allowable other than a 1 week post-operative portal vein infusion of fluorouracil. Written consent was sought before randomisation, and after a full written and verbal explanation of the treatment options had been given. Ethics approval for the study was given by the local research ethics committee at each hospital.

Procedures

QUASAR adopted a pragmatic trial design,[13] with local clinical teams categorising patients as having either a clear or an uncertain indication for adjuvant chemotherapy. The indication for chemotherapy was decided by each patient's clinicians, after consultation with the patient, rather than by any per-protocol definition. In practice, lymph node status was the key discriminant, with 70% of those deemed to have a clear indication for chemotherapy having stage III disease, while 91% of those with an uncertain indication had stage II disease. Data for the patients with a clear indication for chemotherapy have been reported elsewhere.[13] Patients with an uncertain indication for chemotherapy were randomly assigned to receive adjuvant chemotherapy or to observation, but with chemotherapy considered in the event of recurrence. A minimised randomisation procedure was used to ensure that allocations were balanced with respect to age, tumour site, stage, portal vein infusion or not, pre-operative radiotherapy or not, planned post-operative radiotherapy or not, and chemotherapy schedule (weekly or every 4 weeks). Randomisation was done by telephone call to a central office. Until October, 1997, those allocated to receive chemotherapy were simultaneously randomly allocated to receive fluorouracil plus either high-dose or low-dose folinic acid, each combined with levamisole or placebo. Subsequently, all patients allocated to receive chemotherapy received fluorouracil plus low-dose folinic acid.

Chemotherapy consisted of 30 doses of fluorouracil (370 mg/m^2 intravenously) combined with either high-dose (175 mg intravenously) or low-dose (25 mg intravenously) L-folinic acid. L-folinic acid, the active isomer, is equivalent, pharmacologically, to double the dose of racemic folinic acid.[18] It was recommended that chemotherapy be given in six 5-day courses every 4 weeks, but a 30-week schedule of once weekly administration was also allowable.[19] The dose of fluorouracil for subsequent courses was reduced if substantial toxicity occurred after the previous course. Levamisole (50 mg or matching placebo) was given three times daily for 3 days repeated every 2 weeks for 12 courses. Chemotherapy and levamisole or placebo treatment started in the same week, if possible within 6 weeks of surgery. Use of radiotherapy for rectal cancers, and all other aspects of patient management, were left to the discretion of the responsible physician.[13]

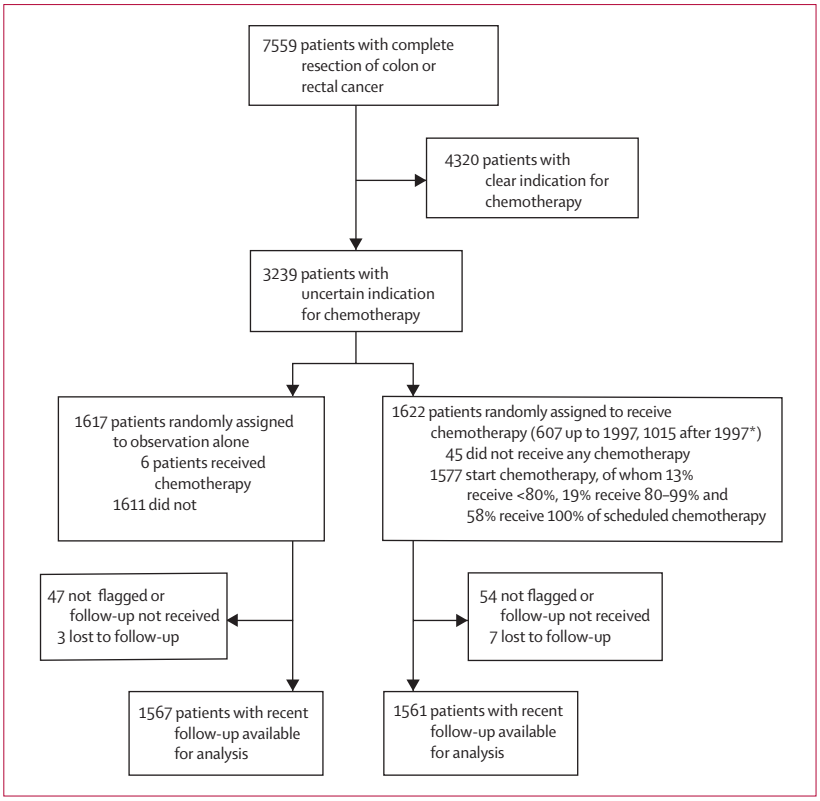

Figure 1: **Trial profile**
*Until October, 1997, chemotherapy was delivered as intravenous fluorouracil (370 mg/m^2) with either high-dose (175 mg) or low-dose (25 mg) L-folinic acid, each combined with levamisole or placebo. After October, 1997, patients who were assigned to receive chemotherapy were given fluorouracil and low-dose folinic acid only.

To facilitate large-scale recruitment, QUASAR adopted a streamlined trial design[13,20] with no extra investigations and minimal extra workload for participating clinicians. Important prognostic data were collected at randomisation. Collaborators were required to notify the trial office of any serious unexpected adverse experiences believed to be due to chemotherapy. But, apart from this, there was just one yearly follow-up form that requested brief details of serious toxicity, recurrence, and death. In the UK, this information was supplemented by use of national mortality records with extra information sought from clinicians on the causes of deaths without recorded recurrence. Flagged patients from England and Wales were assumed to be alive as of January, 2005, unless notified otherwise. A postal follow-up of the status of all patients was done in January, 2004. For analyses of recurrence, and for survival analyses for patients who had not been successfully flagged, analyses were censored at March, 2004, if a follow-up reply was received or at last follow-up otherwise.

Dispensing pharmacists were asked to record the doses and schedule of fluorouracil and folinic acid until 1998,

when central supplies of folinic acid were discontinued. Health economic data, compliance, treatment toxicity, and quality of life were measured in a substudy (n=700, from selected centres in the West Midlands) through patient questionnaires (European Organisation for Research and Treatment of Cancer QLQ-30[21] with colorectal cancer,[22] resource usage modules, and the hospital anxiety and depression scale[23]) completed before chemotherapy and then at 3, 6, 15, and 27 months. Detailed toxicity data were recorded at the same time points from patient notes. Pathological reports were requested retrospectively from all patients. At the time of submission, 650 such reports had been received; these reports were reviewed centrally.

To assess cost-effectiveness as cost per quality-adjusted life-year (QALY), the average life-years gained through improved survival with chemotherapy were estimated by use of UK national mortality statistics and the QALYs lost during chemotherapy by assigning a utility score to quantify the reduction in health-related quality of life while undergoing chemotherapy.

	Chemotherapy (n=1622)	Observation (n=1617)
Stage		
I	8 (0·5%)	8 (0·5%)
II	1483 (91%)	1480 (92%)
III	131 (8%)	129 (8%)
Site		
Colon	1148 (71%)	1143 (71%)
Rectum (or both)	474 (29%)	474 (29%)
Sex		
Male	1006 (62%)	973 (60%)
Female	616 (38%)	644 (40%)
Age (years)		
<50	185 (11%)	185 (11%)
50–59	427 (26%)	428 (26%)
60–69	678 (42%)	673 (42%)
70+	331 (20%)	332 (21%)
Range in years	23–86	23–84
Median age	63 (56–68)	63 (56–68)
Other adjuvant therapy		
Pre-operative radiotherapy	102 (6%)	101 (6%)
Postoperative radiotherapy	133 (8%)	131 (8%)
Portal vein infusion	6 (0·4%)	5 (0·3%)
Intended chemotherapy schedule		
5-day course every 4 weeks	769 (47%)	765 (47%)
Once weekly	853 (53%)	852 (53%)
Chemotherapy allocated		
Fluorouracil+high-dose folinic acid +levamisole*	141 (9%)	NA
Fluorouracil+high-dose folinic acid +placebo*	143 (9%)	NA
Fluorouracil+low-dose folinic acid +levamisole*	142 (9%)	NA
Fluorouracil+low-dose folinic acid +placebo*	141 (9%)	NA
Fluorouracil+high-dose folinic acid†	20 (1%)	NA
Fluorouracil+low-dose folinic acid†	20 (1%)	NA
Fluorouracil+low-dose folinic acid	1015 (63%)	NA
No chemotherapy	NA	1617

Data are n (%) or median (IQR). *Randomised between high-dose and low-dose folinic acid and between levamisole and placebo. †Randomised between high-dose and low-dose folinic acid.

Table: **Baseline characteristics of randomised patients**

Statistical analysis

Target recruitment was at least 2500 patients, which would give a more than 80% chance of detecting a 5% improvement in survival (eg, from 75% to 80%) between chemotherapy (any) and control, at a significance level of less than 0·05. The decision to close recruitment was made by the trial steering committee without knowledge of interim results. The primary outcome measure was all-cause mortality. Secondary outcomes were death from colorectal cancer, and recurrence. Analyses were by intention to treat and used standard log-rank methods. Tests for heterogeneity of treatment effect between subgroups were as described by the Early Breast Cancer Trialists' Collaborative Group,[24] using recurrence as the most statistically sensitive outcome measure. Prior hypotheses were that the monthly 5-day schedule would be more effective than the once-weekly schedule and that chemotherapy within 6 weeks of surgery would be more effective than later.

Analyses were done with SAS version 9.1. This trial is registered with the International Clinical Trial Registry, number ISRCTN82375386.

Role of the funding source

The general structure of the study was designed by the UK Coordinating Committee on Cancer Research (London, UK; now the National Cancer Research Institute), and managed, analysed, and reported independently of the funding body or any companies, who had no representative in its organisation and who, like the steering committee, remained blind to the results as they accumulated. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Results

Between May 25, 1994, and Dec 24, 2003, 3239 patients were entered into the uncertain indication arm of QUASAR by 332 clinicians from 150 centres in 19 countries. Figure 1 shows the trial profile. Patients were well balanced with respect to baseline characteristics (table). The median age of the patients was 63 (IQR 56–68) years; 1979 (61%) were men; 2291 (71%) had colon cancer; 260 (8%) had stage III, 2963 (91%) stage II, and 16 (0·5%) stage I disease. Of the 628 patients with data for vascular invasion and T stage, 81 (13%) had vascular invasion, 78 (13%) had T4 tumours, and 32 (5%) had both. If allocated, chemotherapy was scheduled for

5 days every 4 weeks for 1534 (47%) patients and once a week for 1705 (53%). Chemotherapy was mainly fluorouracil plus low-dose folinic acid (1318 of 1622 patients, 81%) without levamisole (1337 of 1622 patients, 82%), with 0·3% also receiving a postoperative portal vein infusion of fluorouracil. 198 (21%) of the 948 patients with rectal cancer or both rectal and colon cancer had received pre-operative radiotherapy, 202 (28%) of these patients were scheduled for postoperative radiotherapy.

3% (45/1622) of patients allocated chemotherapy did not start (figure 1). Of those who did, pharmacy record cards were available for 742 (47%), with 428 (58%) receiving their full chemotherapy and 558 (77%) at least 80%. In those receiving chemotherapy every 4 weeks, the cumulative dose of fluorouracil was higher for those aged under 70 years than for older patients (17·9 g *vs* 15·6 g, p<0·0001; webtable 1); by contrast, of the patients receiving once-weekly chemotherapy, there was no difference in cumulative dose between those aged under 70 years and older patients (18·3 g *vs* 18·0 g, p=0·09). Radiotherapy use was similar in the chemotherapy and observation groups.

2793 (86%) patients in QUASAR were entered from the UK, of whom 2712 (97%) were successfully flagged with the national death registry, and were thus assumed to be alive as of January, 2005, unless notified otherwise. Replies to the postal follow-up have been received at the time of this report for 2306 (90%) of the 2558 patients still alive. 111 (4%) of the 2558 patients alive had missing follow-up—ie, not flagged or no recent follow-up received. The median follow-up of the surviving patients is 5·5 (range 0–10·6) years.

Over the whole study period, there were 311 deaths in the chemotherapy group and 370 in the observation group. The relative risk of dying from any cause with chemotherapy versus observation was 0·82 (95% CI 0·70–0·95; p=0·008; figure 2). The numbers of deaths from causes other than colorectal cancer were similar in the chemotherapy and observation groups: 77 (4·7%) died in the chemotherapy group versus 86 (5·3%) in the observation group (p=0·3; webtable 2). The relative risk of dying from colorectal cancer was 0·81 (95% CI 0·68–0·96; p=0·01).

There were 293 recurrences in the chemotherapy group and 359 in the observation group. The relative risk of recurrence with chemotherapy versus observation over the whole study period was 0·78 (95% CI 0·67–0·91; p=0·001; figure 2). There was significant heterogeneity in treatment effect by period of follow-up, with 149 (9·2%) recurrences in the chemotherapy group in the first 2 years after randomisation, compared with 227 (14·0%) in those in the observation group (p=0·004). The relative risk of recurrence in the first 2 years with chemotherapy versus observation was 0·64 (95% CI 0·52–0·78; p<0·0001; figure 3). Subsequently, there was no benefit, or loss of benefit, with 144 (12·8%) of 1127 patients in the chemotherapy group and 132 (12·7%) of 1040 patients in the observation group experiencing a recurrence after 2 years (p=0·94).

The proportional reduction in recurrence with chemotherapy versus observation alone was much the same in patients with stage II and in those with stage III cancer, and in patients with colon and those with rectal cancer (figure 3). There was also no significant difference in the effect size between men and women, once-weekly chemotherapy and chemotherapy every 4 weeks, or in time from surgery to randomisation (figure 3). The relative risk of recurrence with chemotherapy compared with observation alone in patients with stage II cancer was 0·78 (95% CI 0·66–0·93; p=0·004) and 0·68 (95% CI 0·52–0·88; p=0·004) in those with rectal cancer (figure 4). There was no reduction in recurrence for patients aged over 70 years, but this apparently lesser treatment benefit with increasing age did not reach statistical significance

See Online for webtables 1 and 2

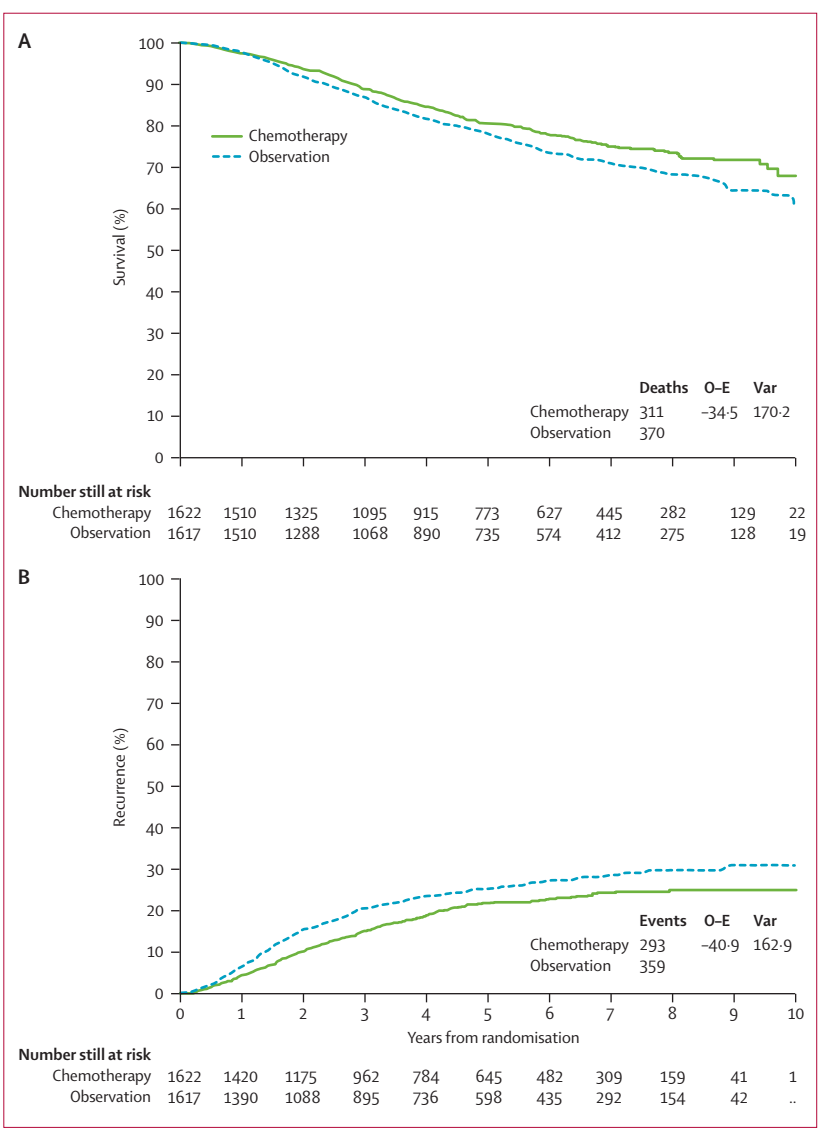

Figure 2: **(A) Risk of all cause mortality and (B) recurrence**

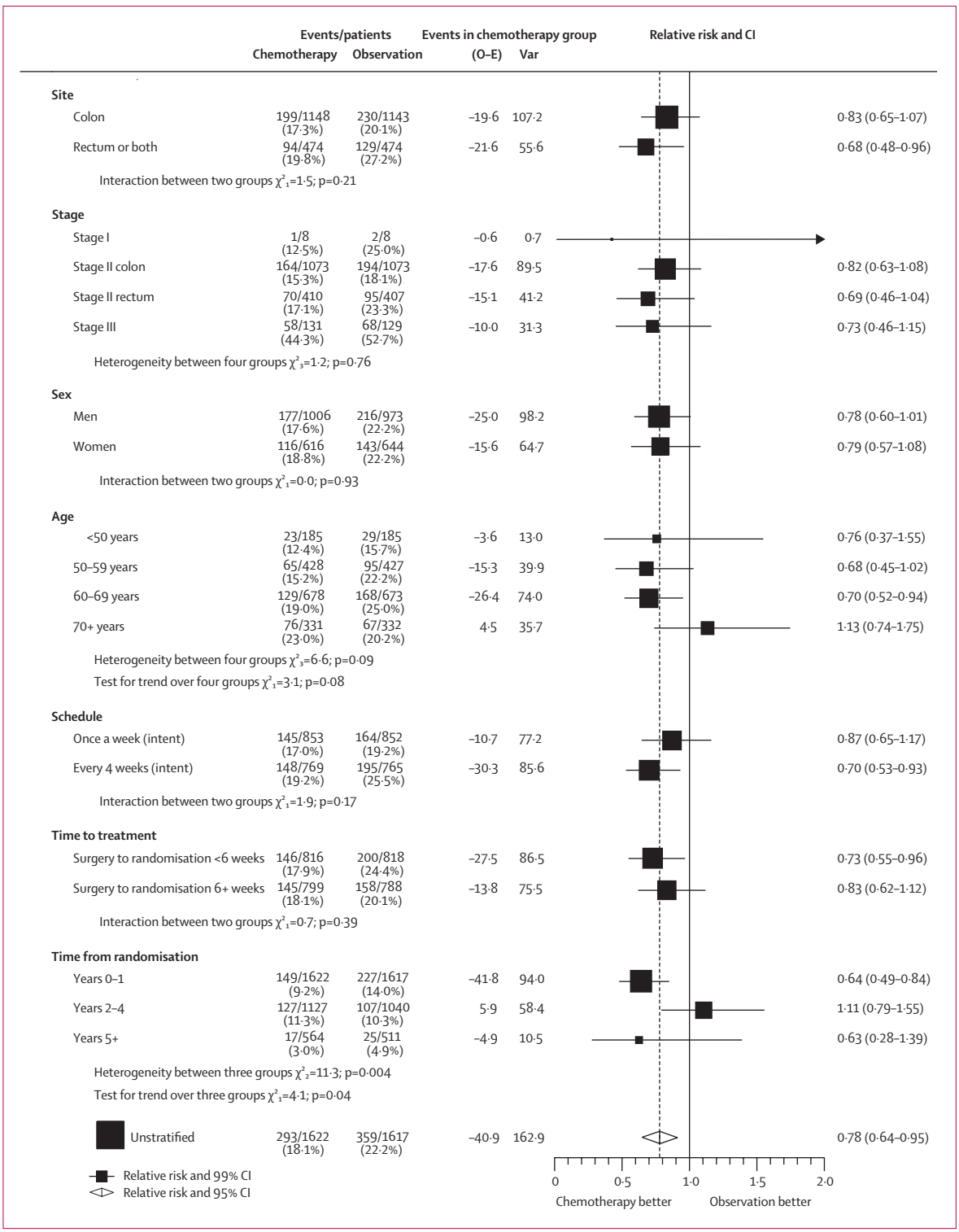

Figure 3: **Relative risk of recurrence with chemotherapy by site, stage, sex, age, chemotherapy schedule, and timing**

(p=0·09; figure 3). Comparison of the proportional reductions in recurrence in the 2 years after randomisation, where the most extreme effect of chemotherapy is seen (figure 3), showed a similar, borderline significant pattern of decreasing benefit with age (p=0·05; webfigure 1). The relative risk of recurrence in the 2 years after randomisation was 0·71 (95% CI 0·54–0·92; p=0·01) for patients with stage II colon cancer

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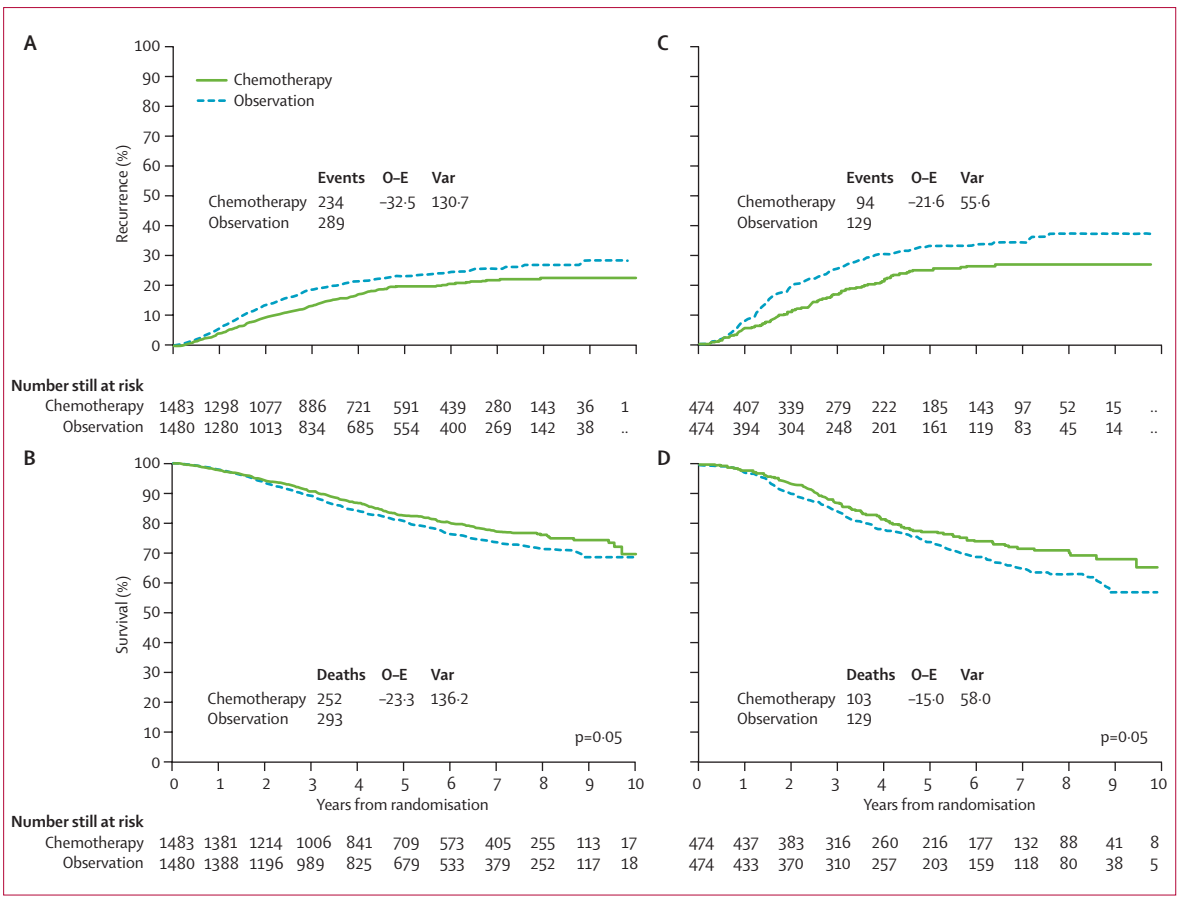

Figure 4: **Effect of chemotherapy on (A) recurrence and (B) survival for stage II patients and on (C) recurrence and (D) survival for patients with rectal cancer**

and 0·57 (95% CI 0·38–0·89; p=0·007) for patients with stage II rectal cancer (figure 5). For patients aged under 70 years, the relative risk of recurrence in the 2 years after randomisation was 0·59 (95% CI 0·43–0·82; p=0·0008) for those with stage II colon cancer and 0·58 (95%CI 0·38–0·93; p=0·01) for those with stage II rectal cancer (webfigure 2).

Subgroup investigations of mortality were less reliable than for recurrence because of the lesser treatment effect, but followed a similar pattern (figure 6). The relative risk of death from any cause in patients with stage II cancer was 0·84 (95% CI 0·68–1·00; p=0·046) and 0·77 (95%CI 0·54–1·00; p=0·05) for those with rectal cancer (figure 4).

Serious, unexpected adverse events were rare: eight (0·5%) patients in the chemotherapy group and four (0·25%) of those in the observation group died from non-colorectal cancer causes within 30 weeks of randomisation (webtable 2). Only one of these deaths was deemed to be possibly chemotherapy related. Quality-of-life measurements directly related to expected toxicity (diarrhoea, nausea, vomiting, mouth pain, fatigue, appetite loss, and social functioning) were worse in those patients in the chemotherapy group than in those in the observation group (p<0·001 for all categories), but only during chemotherapy. Chemotherapy patients with clinician-rated grade 3/4 toxicity reported worse global quality of life than did those with lesser or no toxicity. The only material difference between chemotherapy regimens was between schedules with more grade 3/4 toxicity with the four-weekly than the once-weekly schedule. The proportion of patients with grade 3/4 nausea (6% of 200 patients *vs* 1% of 227 patients), oral adverse events (10% *vs* 0%), diarrhoea (11% *vs* 5%), neutropenia (7% *vs* 1%), and any grade 3/4 toxicity (31% *vs* 10%]) was significantly greater with 4-week courses of chemotherapy than with once-weekly delivery (p<0·001 for all adverse events; webtable 3).

See Online for webfigure 2

See Online for webtable 3

Resource usage, other than for chemotherapy administration, did not differ between patients randomised to chemotherapy and observation. The cost of delivering QUASAR chemotherapy was estimated to be between £2000 and £3000 per person. A utility score for QUASAR chemotherapy was not measured directly, but in view of the minor effect of chemotherapy on quality of life, was estimated to be 0·7 during the 6 months of chemotherapy—ie, a loss of about 8 weeks of full health life. Sensitivity analyses indicate that the two chief determinants of cost per QALY are the size of survival

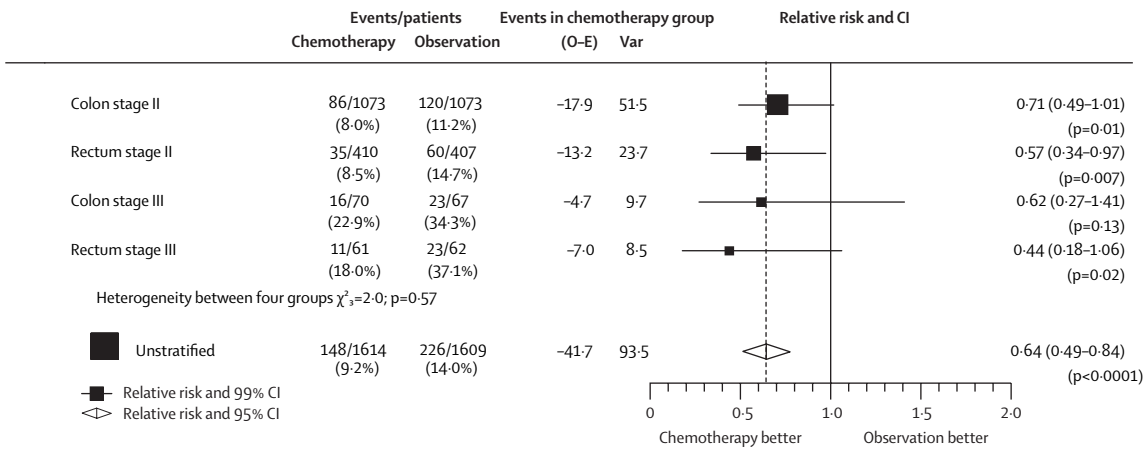

Figure 5: **Relative risk of recurrence in first 2 years after randomisation by stage and site**

benefit from chemotherapy and the life expectancy (ie, age) of the patient (webfigure 3). For patients under the age of 70 years, there was a net gain of a few months of QALYs even with the lowest estimate of treatment efficacy. By the age of 80 years, only at the highest estimate of treatment efficacy was a small net benefit seen.

See Online for webfigure 3

Discussion

The results presented here indicate that, relative to observation alone, adjuvant chemotherapy with fluorouracil and folinic acid lowers the risk of all-cause mortality in patients with colorectal cancer who have had successful resection of the cancer, and who have an uncertain indication for chemotherapy, by almost a fifth. Of particular interest is the evidence of an improvement in survival with chemotherapy for patients with stage II cancer. Although this improvement was of borderline statistical significance, the survival benefit is supported by a significant reduction in recurrence, by evidence that 3-year disease-free survival is a good surrogate for overall survival,[25] by unequivocal evidence from previous trials of a survival benefit for stage III patients,[26] by evidence from pooled analyses of other randomised trials,[27,28] and from individual studies[3,29] that suggest that the proportional reductions in mortality and recurrence from adjuvant chemotherapy based on fluorouracil are much the same in patients with stage II and III disease. The data presented here are also consistent with previous trial evidence, a meta-analysis of which found a mortality risk ratio of 0·87 (95% CI 0·73–1·01; p=0·07) for patients with stage II disease.[30]

There is also evidence that, relative to observation alone, the risk of death or recurrence in patients with rectal cancer who received adjuvant chemotherapy was lowered, indicating that the previously reported lack of benefit in this subgroup[3] was probably falsely negative. In QUASAR, the effect of chemotherapy on recurrence was larger, albeit not significantly so, in patients with stage II rectal cancer than it was in those with stage II colon cancer. The reduction in stage II colon cancer did not reach statistical significance (figure 3), but this could be explained by the the limited statistical sensitivity of such subgroup investigations,[20] particularly when subdividing analyses by disease stage and then again by site. Comparisons of recurrence rates in the first 2 years after randomisation—the period when the full effect of chemotherapy is seen—are statistically more reliable than are comparisons of all events. The relative risks of recurrence in the first 2 years were similar in patients with stage II colon cancer and in those with stage II rectal cancer (figure 5).

Although probably real, the survival benefit from chemotherapy for a patient with stage II colorectal cancer is small: if 5-year mortality without chemotherapy is 20%, a reduction in the relative risk of death of 18% (95% CI 5–30) translates into an absolute improvement in survival of 3·6% (1·0–6·0). One encouraging finding is that—by contrast with a recent trial report[31]—chemotherapy seems to prevent a proportion of recurrences and deaths, rather than just delaying them, which makes the life-years gained more substantial, especially for younger patients. For example, for a 55-year-old, who would have a life expectancy of 30 more years if not dying of their cancer, reducing their 5-year risk of cancer death by 3·6% (eg, from 20% to 16·4%) would increase their life expectancy by about a year. By contrast, a sustained 3·6% improvement in survival for a 75-year-old, with a life expectancy of about 10 years, would increase their life expectancy by only 4 months. If a 2-month deduction is made for loss of quality-adjusted life during chemotherapy, the average QALYs gained are 10 versus 2 months. Furthermore, the results presented here suggest that the proportional reduction in mortality with chemotherapy is less for older patients. However, this finding could be a false negative, since other studies have reported benefit for

patients over the age of 70 years.[32,33]

Current recommendations are that patients with stage II disease who have a higher than average risk of tumour recurrence—eg, those with stage T4 disease or vascular invasion, about 30% of the QUASAR study population—should be offered chemotherapy.[16] Pathological data were available for only 20% of the study population, and so any difference in efficacy between those with high-risk stage II disease and those with low-risk stage II disease could not be investigated.

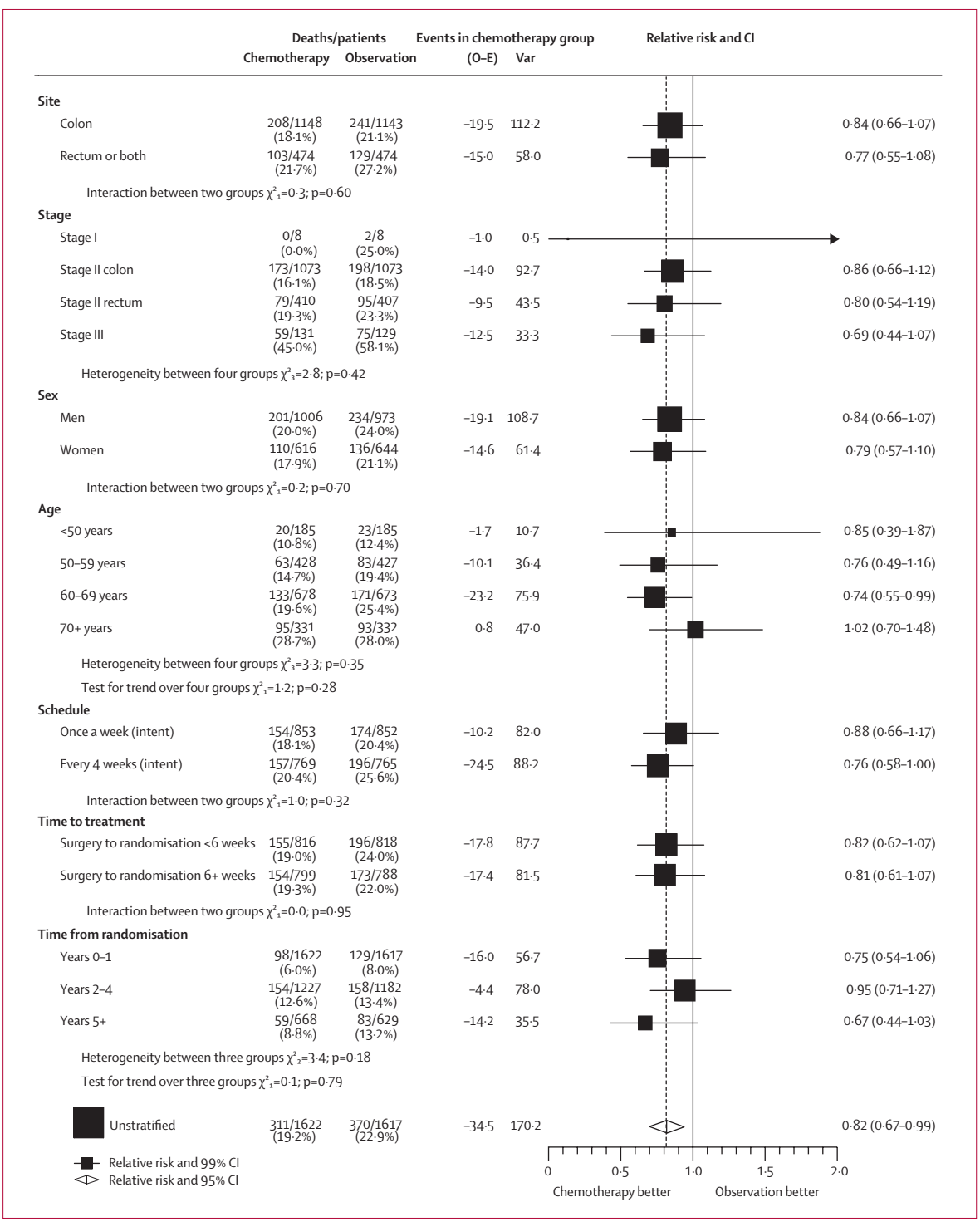

Figure 6: **Relative risk of death with chemotherapy by site, stage, sex, age, chemotherapy schedule, and timing**

However, the similar proportional reductions with chemotherapy in the risk of recurrence in patients with stage II disease and those with stage III disease suggest that the proportional reductions in the risk of recurrence in high-risk and in low-risk stage II disease will also be similar. Thus, because pathological variables are only moderately prognostic of outcome in stage II disease, they are only moderately useful as discriminants of treatment benefit. For example, preliminary analyses of pathological data from QUASAR suggest that the 5-year risks of death for an untreated patient with stage II disease with and without high-risk features are about 30% and 20%, respectively (data not shown). The absolute benefit from an 18% reduction in mortality would be 5·4% in those with high-risk features and 3·6% in those without, which might both be considered sufficient to justify well-tolerated QUASAR-type chemotherapy,[34] at least for younger patients. Reliable predictors of sensitivity to chemotherapy would constitute a more useful means to help individualise adjuvant therapy. QUASAR includes a substudy of stored cancer tissue that will help clarify the role of high-risk factors in stage II disease and, hopefully, identify tumour markers that will enable targeting of treatment at the most responsive patients.

See Online for webappendix

The optimum chemotherapy regimen for stage II disease is unclear. 20% of patients in QUASAR received levamisole or high-dose folinic acid, or both, but this has no relevant effect on interpretation of the study findings because neither the addition of levamisole nor use of a higher dose of folinic acid had any effect on the efficacy of the combination of fluorouracil and folinic acid.[10,12,13] Treatment every 4 weeks had a larger effect on recurrence than did the once-weekly regimen; however, the once-weekly regimen was less toxic. Furthermore, the two schedules seemed to have similar efficacy in patients in QUASAR who had a clear indication for treatment.[19] If treatment every 4 weeks is more effective than the once-weekly schedule then the benefits from an optimum chemotherapy regimen will be larger than reported here. Similarly, enhanced survival benefits might be achieved with newer chemotherapy regimens that are more efficacious at preventing recurrence than is the combination of fluorouracil and folinic acid.[35–37] However, whether these newer regimens produce a worthwhile extra survival benefit has yet to be established. Furthermore, safety is a major consideration in choosing adjuvant chemotherapy, in particular for patients at low risk of recurrence. There have been five toxicity-related deaths—all receiving treatment every 4 weeks[13]—in almost 6000 patients treated with chemotherapy in QUASAR, considerably fewer than reported with newer chemotherapy regimens.[35–39]

The small but definite benefit from well-tolerated chemotherapy found here should provide helpful new information for discussions between patients and physicians on the potential benefits of chemotherapy, and allow the patient to make a better informed decision to proceed with, or refuse, the offer of chemotherapy. Longer follow-up of QUASAR, and meta-analysis with other studies, is needed to resolve whether chemotherapy produces worthwhile benefits for those aged over 70 years, and further trials are needed to define the optimum chemotherapy regimen.

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Conflict of interest statement

None of the writing committee members have any conflict of interest to declare.

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