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Original article

Adjuvant chemotherapy with 5-fluorouracil, L-folinic acid and levamisole for patients with colorectal cancer: Non-randomised comparison of weekly *versus* four-weekly schedules – less pain, same gain

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Summary

Background: QUASAR is a large trial of adjuvant chemotherapy for colorectal cancer in which clinicians could choose to deliver a standard adjuvant cytotoxic chemotherapy regimen, 5-fluorouracil (5-FU) and L-folinic acid (L-FA), in either a once-weekly or a four-weekly schedule. We report results of a non-randomised comparison between these schedules with respect to survival, recurrence and differential toxicity.

Patients and methods: In a factorial (2 × 2) trial design, QUASAR compared high-dose (175 mg) *versus* low-dose (25 mg) L-FA and levamisole *versus* placebo. The dose of 5-FU was fixed at 370 mg/m^2 and although the recommended schedule was i.v. bolus delivery, daily for 5 days repeated four-weekly for 6 months, a significant proportion of randomising clinicians were constrained to deliver once-weekly 5-FU–L-FA for 30 weeks.

Results: Four thousand nine hundred twenty-seven patients were entered into QUASAR between May 1994 and October 1997, eighteen hundred twenty-nine of whom have recurred and sixteen hundred eighty-nine died. Similar numbers 2370 vs. 2559 were treated with the once-weekly and four-weekly schedules and the demographic features of the 2 groups were well balanced: stage C, 73.3% once-weekly vs. 71.0% four-weekly; colon, 68.0% vs. 68.3%; high-dose FA, 50.1% vs. 49.9%; levamisole, 49.3% vs. 49.3%; females, 40.2% vs. 41.7%; median age (years) 62 vs. 61. The risk of recurrence and survival were similar regardless of schedule: three-year survival was 70.6% once-weekly vs. 71.0% four-weekly; three-year recurrence risk was 35.6% once-weekly vs. 35.5% four-weekly; But, the once-weekly regimen was much less toxic: number of patients for whom toxicity was reported (once-weekly: four-weekly), stomatitis, 37 vs. 337; diarrhoea, 260 vs. 440; neutropenia, 20 vs. 153.

Conclusions: The once-weekly regimen is much less toxic than and, apparently, about as effective as the four-weekly schedule. This suggests that the toxicity of 5-FU–L-FA adjuvant chemotherapy could be reduced substantially by weekly scheduling without compromising efficacy. Alternatively, efficacy might be enhanced with equal toxicity by more dose-intense weekly FU–L-FA regimens. However, this conclusion from a non-randomised comparison needs confirmation in prospective randomised studies.

Key words: adjuvant chemotherapy schedule, colorectal cancer, 5-fluorouracil, folinic acid, randomised controlled trial

Introduction

Cancer of the colon and rectum is a common malignancy in Europe and the United States, second only to lung in men and breast in women. It is estimated that there are 700,000 new cases and 500,000 deaths world wide each year [1]. Surgery remains the primary treatment in approximately 75% of presenting patients. However, about half of resected patients develop recurrent disease which is ultimately fatal. There is a definite role for adjuvant chemotherapy for Dukes' C colon patients following resection, with encouraging results (absolute survival benefit of about 5%–6% in favour of the treatment arms) but continued controversy about the role of systemic cytotoxic therapy for rectal and Dukes' B colon cancer patients [2–8]. 5-fluorouracil (5-FU), first developed as an anticancer drug four decades ago, is the therapeutic mainstay for colorectal cancer, but insights into pharmacokinetic and pharmacodynamic modulation of its activity [9] mean that there is fertile ground for clinical research aimed at developing optimal 5-FU–folinic acid (L-FA) schedules to deliver most health gain with least toxicity.

It was against this background that the QUASAR ('Quick And Simple And Reliable') trial was designed to provide large-scale randomised evidence on the true value of different adjuvant chemotherapy regimens amongst different types of patient. There were two linked components in QUASAR. One, which is still in progress and is not the subject of the present report, compared adjuvant *versus* no adjuvant therapy. The second, which is the largest randomised trial yet reported of any type of cancer treatment, compared various different 5-FU–L-FA based adjuvant regimens against each other to determine whether levamisole and/or higher-dose FA would confer additional benefit [10].

As an anti-metabolite, 5-FU is both S-phase and cell cycle specific. Therefore it follows that prolonged expo-

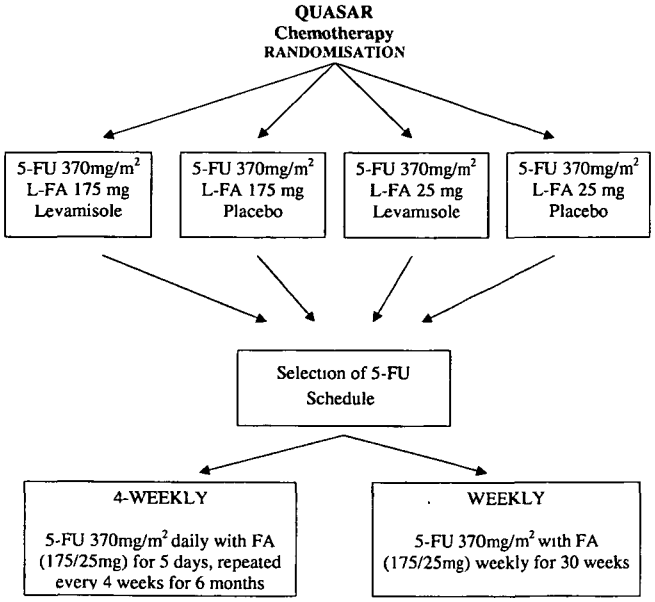

Figure 1 Trial structure, randomisation options and 5-FU schedules.

sure is theoretically much more likely to be cytotoxic than intermittent brief exposure [11, 12]. There are some clinical data supportive of this cell kinetic hypothesis in that prolonged continuous infusions of 5-FU double the response rate and have a marginal survival benefit compared to weekly bolus 5-FU for patients with advanced cancer [13, 14]. For similar reasons it has also been assumed that the standard frequent-intermittent regimen, 5-FU and FA by i.v. bolus daily for five days repeated four-weekly would be more effective than an infrequent intermittent regimen, and so this was recommended in QUASAR. But if this schedule was locally impracticable (e.g., because of peripatetic weekly clinics), then the 5-FU–L-FA could be administered once weekly. Although no randomised comparison between once-weekly and four-weekly regimens have been undertaken it was anticipated on theoretical grounds that once weekly would not be as effective, and the QUASAR protocol therefore specified the prior hypothesis that the 4-weekly schedule would be more effective than the weekly regimen.

The randomised comparisons in QUASAR have been reported and suggest that there are no survival differences between high dose and low-dose FA or between levamisole and placebo [10]. This simplifies the comparison between schedules and we report here this non-randomised comparison between once-weekly and four-weekly treatment schedules.

Patients and methods

Patients

The QUASAR trial design and procedures are described in detail elsewhere [10]. In brief, patients were eligible if they were thought by the responsible clinician to have had a complete resection of colorectal cancer with no evidence of distant metastases, and to have no definite contraindications to any of the chemotherapy regimens in Figure 1.

Table 1. QUASAR dose reductions for toxicity: the percentage of the 5-FU dose used in the preceding course which should be given for all further courses of therapy.

Haematological toxicity	Non-haematological toxicity (diarrhoea, stomatitis)			
CTC grade	0–1	2	3	4
0–2 (P ≥ 50 and N ≥ 1.0)	100	80	50	NFT
3 (P = 25–49 or N = 0.5–0.9)	80	70	50	NFT
4 (P < 25 or N < 0.5)	50	50	50	NFT

Abbreviations: P – platelets; N – neutrophils; NFT – no further treatment recommended.

Drug regimens

All chemotherapy patients received a total of 30 doses of 370 mg/m² i.v. of 5-FU combined with either high-dose (175 mg i.v. fixed dose) or low-dose (25 mg i.v. fixed dose) L-folinic acid. L-folinic acid, the active isomer, is equivalent, pharmacologically, to double the dose of D,L-folinic acid [15, 16]. The chemotherapy tested was a practicable outpatient regimen involving either 6 five-day courses at four-weekly intervals or, alternatively, a once-weekly schedule for 30 weeks. The choice of schedule was decided by the clinician and recorded prior to randomisation. In the event of toxicity between courses (on either schedule), the dose level of 5-FU for all subsequent courses was reduced depending on the worst grade of toxicity observed following the previous course using a standardised dose reduction scheme (Table 1).

Patients were also randomised between levamisole and placebo. Levamisole was given at 50 mg three times daily for three days repeated at two-weekly intervals for 12 courses. Chemotherapy and levamisole/placebo treatment started in the same week, if possible within six weeks of surgery.

Radiotherapy

The use of radiotherapy was left to the discretion of the responsible physician. It was, however, recommended that any radiotherapy should be given pre-operatively [17]. If post-operative radiotherapy was preferred, then the chemotherapy regimen was slightly modified. On the weekly FU–FA regimen, radiotherapy was given without any interruptions of chemotherapy but with the 5-FU dose reduced to 300 mg/m² during the period of radiotherapy. In the four-weekly schedule one five-day course of chemotherapy was substituted with a five-week course of once-weekly chemotherapy during radiotherapy, again with 5-FU at 300 mg/m². There was then a treatment-free interval of four weeks before the remaining five-day courses of chemotherapy were given. The levamisole regimen was unaffected by any radiotherapy.

Minimal data collection

To facilitate large-scale recruitment, QUASAR imposed little or no extra workload on participating clinicians, beyond that required to treat their patients. Randomisation was by a short telephone call, during which the relevant patient characteristics were recorded, so there was no entry form.

Collaborators were required to notify the trial office by telephone of any serious unexpected adverse experiences believed to be due to chemotherapy. Apart from this, there was just one annual follow-up form, requesting brief details of serious toxicity, recurrence and death.

Investigators were, however, asked to provide further details of causes of death for patients dying without recorded recurrence. This information was supplemented by the use of national mortality records to help ensure the completeness of long-term follow-up. Also, pharmacists were supplied with a QUASAR pad to record the treatment pack used and the 5-FU dose and schedule. Copies of these pads were sought once patients had completed chemotherapy. Health economic data, compliance, detailed treatment toxicity and quality of life were assessed, for about 10% of patients, in a sub-study (which will be reported separately).

Statistical considerations

QUASAR aimed to randomise 5000 patients between the four chemotherapy regimens in order to give at least an 80% power to detect a difference of 5% in survival (e.g., 50%–55%) from using the higher dose of FA or from adding levamisole to 5-FU–FA. The main endpoint was all cause mortality Subsidiary endpoints were (a) recurrence risk and (b) deaths from colorectal cancer. In both of these, deaths due to other causes without recurrence were ignored. Standard log-rank methods were used for these comparisons. Odds of death and recurrence and the tests for heterogeneity of treatment effects between subgroups use methods described by the EBCTCG [18]. There was a prior hypothesis that the four-weekly five-day schedule would be more effective than the once-weekly schedule.

Follow-up

Ninety-five percent of patients were entered from the UK. Of these, 94% were successfully flagged with the national death registry and copies of death certificates for all such patients dying were sent to the trial office, usually within three months. Flagged patients are assumed to be alive as of 30 November 1999 unless notified otherwise. In addition, a postal follow-up of the status of all patients was undertaken in 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 are censored at 30 June 1999. The median follow-up of the surviving patients is 3.6 years.

Results

Patient characteristics

Although this is a non-randomised comparison, patients were well balanced with respect to baseline characteristics (Table 2). The median age was 62 years, 41% were female, 68% had colon cancer, 72% had Dukes' C (node positive disease) and patients were of similar body mass (median surface area 1.8 m^2). Similar numbers had pre- or post-operative radiotherapy.

The comparisons between groups were also closely balanced with respect to the randomised comparators (dose of L-FA and levamisole–placebo) as a minimised randomisation procedure was used thereby ensuring that the trial treatments were evenly balanced with respect to participating centre, patient demographics, chemotherapy schedule (once-weekly, four-weekly) and indication (clear/uncertain). Other aspects of patient management were also similar as randomised treatments were double blinded. Choice of chemotherapy schedule was left to the responsible clinician but was stated prior to randomisation. Investigators generally opted for one or the other schedule for administrative reasons with 79 clinicians using weekly only (769 patients) and 98 using four-weekly only (1088 patients). Twenty-eight doctors used one almost exclusively (1426 patients) whereas the remaining 81 doctors used both schedules intermittently. It might be expected that the choice of schedule for this latter group of doctors would be determined at least to some degree by patient selection factors. However, the breakdown of risk factors by treatment schedule for intermittent users only shows no marked differences in prognostic variables with, if anything more high risk (stage C) patients receiving the less toxic once-weekly schedule. Nor, as might be expected, are more older patients receiving once-weekly chemotherapy. There is, however, a highly significant secular trend towards use of once-weekly schedule in the latter part of the trial. This indicated that the main reason why some clinicians used both schedules was a developing preference for the less toxic regimen for all patients rather than selective use for particular patients. If so, this reduces the probability of any substantial selection bias.

Table 2. Patient characteristics.

	Four-weekly, % (n = 2557)	Weekly, % (n = 2370)	P-value
Mean age (years)	61	62	
Mean surf area (m^2)	1.80	1.81	
Females	41.7	40.2	0.28
Colon	68.3	68.0	0.82
Dukes' C	71.0	73.3	0.07
Pre-op RT	3.3	4.6	0.02
Planned post-op RT	16.9	16.0	0.23
High-dose folinic acid	50.1	49.9	
Levamisole	53.2	46.8	
Portal vein infusion	0.4	0.5	0.46
Clear indication	87.2	88.2	0.28
Year randomised			
1994	8.2	8.6	0.62
1995	35.4	31.7	<0.01
1996	43.8	45 9	0.14
1997	12.7	13.8	0.26

Recurrence and survival

There was no discernible difference in recurrence rates between the weekly and four-weekly schedules (Figure 2) with similar numbers of recurrences in both groups (874 of 2370 vs. 955 of 2557). The three-year risk of recurrence was 35.6% for the once-weekly group and 35.5% for the four-weekly group. The odds of recurrence in the four-weekly schedules was 0.99 (95% confidence interval (95% CI): 0.90–1.08).

The odds of recurrence for the two groups with respect to a range of subgroup analyses (site, stage, gender and age) are summarised in Figure 3. There are no significant subgroup effects on recurrence rates.

Survival is shown in Figure 4. Again, there is no discernible difference in survival between the two

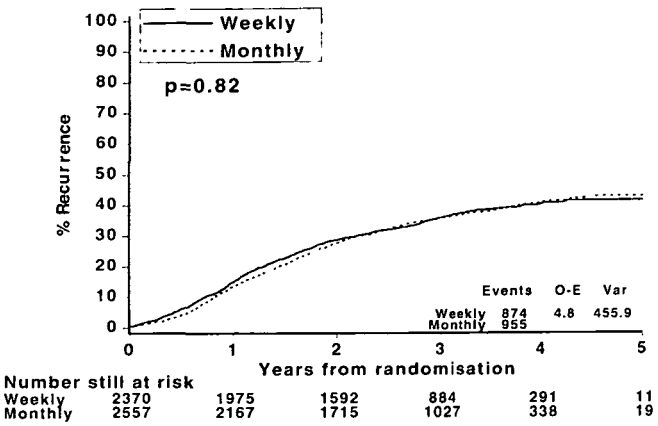

Figure 2. Five-year recurrence risk of 4927 patients, weekly *versus* four-weekly schedule.

Table 3. Number of patients reported to be suffering toxicity.

	Four-weekly	Weekly	Odds ratio	95% CI	*P*-values
Diarrhoea	440	260	1.69	1.43–1.99	<0.001
Stomatitis	337	37	9.57	6.78–13.51	<0.001
Vomiting/nausea	174	144	1.13	0.90–1.42	0.30
Neutropenia	154	20	7.53	4.71–12.04	<0.001
Other haemato-logical	40	14	2.67	1.45–4.93	0.001
Dermatological	122	52	2.23	1.61–3.11	<0.001
Cardiovascular	42	37	1.05	0.67–1.64	0.82
Neurological	23	21	1.02	0.56–1.84	0.97

groups (822 of 2370 vs. 867 of 2557). Three-year survival was 70.6% with the once-weekly and 71.0% with four-weekly schedule. The odds of death in the four-weekly group compared to weekly was 0.97 (95% CI: 0.88–1.06).

The odds of survival for the two groups with respect to a range of subgroup analyses (site, stage, gender and age) are summarised in Figure 5. Again, there is no good evidence in any of the groups that four-weekly is superior to weekly scheduling and minor differences in survival for younger patients (<50 years) in favour of the four-weekly regimen are not statistically significant and could well be chance findings given the number of subgroup investigations undertaken.

Toxicity

Reported toxicity from annual follow-ups and spontaneous reporting of adverse events is shown in Table 3. There are highly statistically significant differences in toxicity which greatly favour the weekly schedule, with 69% more diarrhoea, ($P < 0.001$) nine times more stomatitis ($P < 0.001$) seven times more neutropenia ($P < 0.001$) and twice as much dermatological toxicity ($P < 0.001$). Although toxicity data were not systematically sought for all patients (detailed toxicity, quality of life and health economic data are collected in a subset of 600 patients), the large differences seen between the two schedules could not plausibly be attributed to any reporting bias.

To assess the risk of treatment related fatal toxicity, all deaths, without recorded recurrence that occurred within nine months of randomisation were reviewed in detail to ascertain the cause of death. Only five deaths were adjudged to be toxicity related, all of which were among patients on the four-weekly schedule. It should be noted, though, that the 0.2% treatment related mortality seen with the four-weekly schedule in QUASAR is comparatively low, particularly given the setting of a large, pragmatic multi-centre trial.

Table 4. Dose delivery data.

	Four-weekly	Weekly	*P*-values
Number of patients	1606	1439	
Percentage of patients who underwent 5-FU dose reduction (≤80%)	42	17	<0.001
Percentage of patients who completed ≥28 doses of 5-FU	75.3	73.6	0.28
Median total dose of 5-FU delivered (g)	16.8	18.3	<0.001
Median % of planned dose delivered	85	95	<0.001
Median dose intensity (mg/m^2/week)	398	345	<0.001

5-FU dose reductions, intensity and dose delivered

Pharmacy data sheets which recorded the dose of 5-FU administered were obtained for 80% of patients. As there were protocol specified recommendations that individual consultants should reduce, or omit, the dose of 5-FU during postoperative radiotherapy, patients scheduled for post-operative radiotherapy have been omitted from this analysis. The data are summarised in Table 4.

Far more patients underwent dose reduction (to 80% or less of starting dose) in the four-weekly (42%) compared to weekly (17%) schedule, although the dose reductions appeared effective as the proportions of patients eventually completing the planned course of treatment of 5-FU were similar (75.3% vs. 73.6%). The majority of dose reductions occurred following cycle 1 in the four-weekly regimen (Figure 6) but were more evenly spread over the entire treatment course for weekly administration. The time course of the percentage of patients stopping therapy prematurely shows a rather different pattern with a smooth 'stopping' rate for weekly, whereas the four-weekly schedule, naturally, reveals a stepped reduction after cycle 1 (Figure 7a,b).

Discussion

Analysis of the randomised comparisons in the QUASAR trial suggests that there were no survival benefits accrued

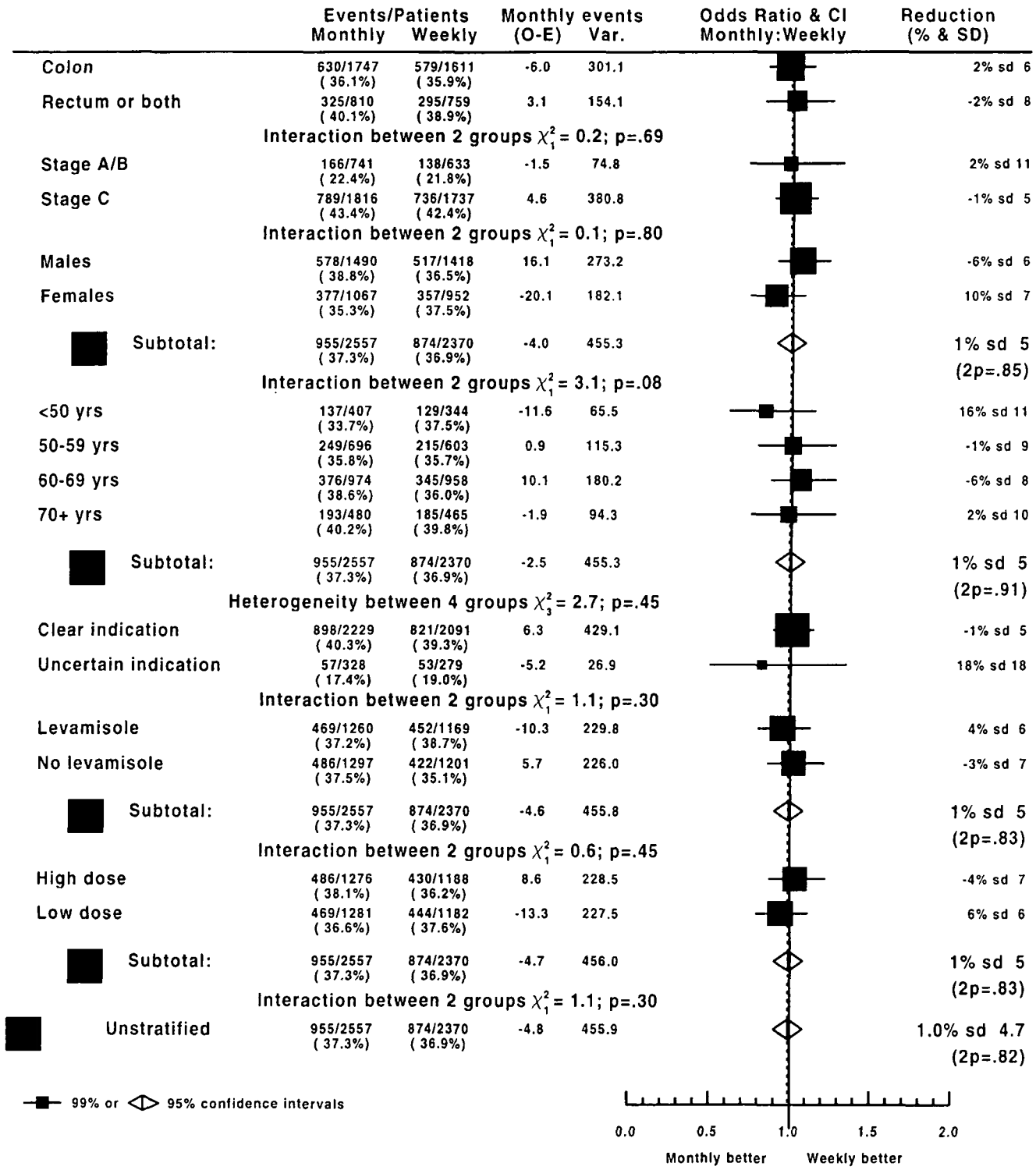

Figure 3. Effect of schedule on the risk of recurrence by site, stage, sex, age and treatment subgroups.

from treatment with high-dose FA or from adding levamisole to 5-FU–L-FA [10]. In this report we show that there is also no apparent difference in recurrence rates or survival when we compare weekly and four-weekly schedules of 5-FU and FA. This is a non-randomised comparison and therefore must be treated with considerable caution, but there are a number of features of the trial which are likely to reduce any systematic bias; the chemotherapy options (high-dose vs. low-dose FA and levamisole vs. placebo) were all double blinded and balanced between schedules at randomisation; demographic factors which have the potential to influence prognosis were very evenly balanced in the treatment groups.

Although recurrence and survival do not appear to be schedule dependent in QUASAR, there is an important difference in toxicity comparing the weekly and four-weekly schedules. There were highly significantly

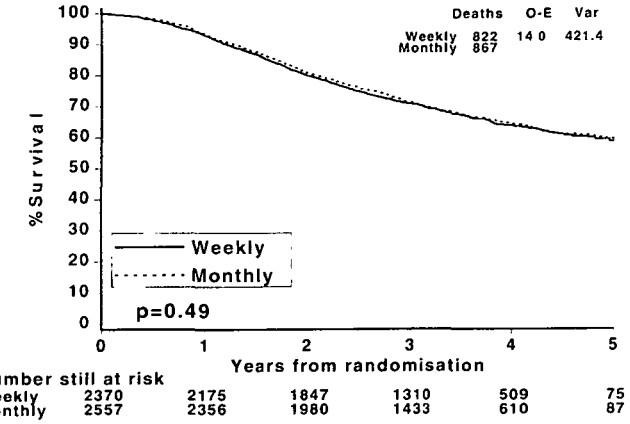

Figure 4. Five-year survival for 4927 patients, weekly *versus* four-weekly schedule.

increased rates of stomatitis (OR 9.6), neutropenia (OR 7.5) and diarrhoea (OR 1.7) for the five-day bolus regimen. This was also manifest in an increased fraction of patients undergoing dose reductions (42% vs. 17%), most of which occurred following the first cycle of therapy in the four-weekly group (Figure 6). At one level, the dose reduction scheme was effective, as the proportion of patients who went on to complete the planned course of treatment of 5-FU was similar for four-weekly (75.3%) and weekly (73.6%) schedules. The projected total dose of 5-FU delivered in both regimens was 11.1 g/m^2 (or about 20 g, given median body surface area of 1.8 m^2), although the planned dose intensity of the four-weekly schedule was higher (463 mg/m^2/week) compared to weekly (370 mg/m^2/week). The median total dose of 5-FU delivered was higher in the weekly regimen (18.3 g vs. 16.8 g, $p < 0.001$) Table 4, whereas the actual dose intensity was higher in the four-weekly regimen (398 mg/m^2/week vs. 345 mg/m^2/week, $P < 0.001$).

The uneven pattern of toxicity following treatment in the four-weekly schedule, skewed significantly towards first cycle dose reductions (Figure 6), has been reported in trials of advanced colorectal cancer [19]. Interestingly, recent analysis of randomised trials in advanced colorectal cancer [20] shows that serious toxicity consequent to cycle 1 treatment with 5-FU, 425 mg/m^2 and D,L-folinic acid, 20 mg/m^2, daily for 5 days (repeated four-weekly) was more common in the elderly (> 70 years) and women. This phenomenon was partly seen in QUASAR in that dose reductions were more common in females (35% vs. 27%; $P < 0.0001$), as was toxicity: diarrhoea (OR = 1.46; $P < 0.0001$), stomatitis (OR = 1.59; $P < 0.0001$), and neutropenia (OR = 1.34; $P = 0.08$). However, dose reductions, or toxicity, were not significantly increased for patients over 70: OR = 1.13; $P = 0.18$.

There is some evidence to suggest that six months adjuvant therapy is as effective as one-year's treatment [21], which is an important observation given the frequent patient attrition in adjuvant trials. In the present study, 70% of patients completed the full course of treatment with the majority of patients coming off treatment in the second three months (Figure 7b). The apparent dip at the end of each curve was due to odd individual doses being missed because of public holidays, etc. Dose reductions for conventional toxicity do not reflect this pattern (Figure 7a), with an even decrement in 5-FU dose with time, apart from the stepped decrease in dose following the first cycle of the four-weekly treatment. This implies that there may be underlying chronic or cumulative toxicity which is not amenable to the dose reduction scheme used to compensate for acute toxicity. There was no obvious excess of cardiac or neurological events, but cumulative fatigue is often under-reported and may have been a contributory factor.

The concept of dose intensity and its importance to outcome in adjuvant trials of colorectal cancer has been reviewed [22]. In that analysis the authors attempted to relate the planned, total dose of 5-FU to outcome of adjuvant chemotherapy for Dukes' B and C colorectal cancer using available published trials. They found that the greatest improvement in survival was in studies in which the largest dose of 5-FU was planned, particularly over the first three months. Their review excluded trials involving 5-FU and folinic acid, they did not obtain individual data sets from the trials involved in their analysis and data on the actual dose administered were not available.

There is no clear consensus as to the optimal combination schedule of 5-FU and FA to be used in an adjuvant setting for colorectal cancer patients. A number of different regimens have been used [2–8], but there are no randomised comparisons, apart from QUASAR, which have controlled for drug dose (either 5-FU or FA) or schedule using bolus administration. There are trials underway, or recently completed, exploring bolus vs. prolonged infusional 5-FU regimens, building on interesting results in advanced disease [13, 14], but these have not yet been formally reported.

At first glance these results seen somewhat surprising. Not the differential toxicity in favour of the weekly schedule, but rather the fact that both schedules seem to be equally effective in terms of recurrence and survival. There is good pre clinical evidence that 5-FU is most effective at killing dividing cells in the DNA synthetic or S-phase of the cell cycle [11, 12]. This applies both *in vitro* and *in vivo,* but raises the question of comparability or relevance of murine tumour model systems to solid human tumours given the large differences in cell growth kinetics. Nevertheless, when prolonged infusions of 5-FU have been compared to bolus therapy in patients with advanced colorectal cancer, meta-analysis of randomised clinical trials shows a significant increase in tumour response and marginal survival benefits for extended exposure to 5-FU, in keeping with the cell kinetic hypothesis [14]. There is less evidence to show that frequent intermittent schedules are superior to infrequent intermittent schedules. In a literature review of all published data of FA and 5-FU intravenous bolus therapy in advanced colorectal cancer with comparable dose intensity, an attempt was made to characterise the possible differences of the variations of schedules used

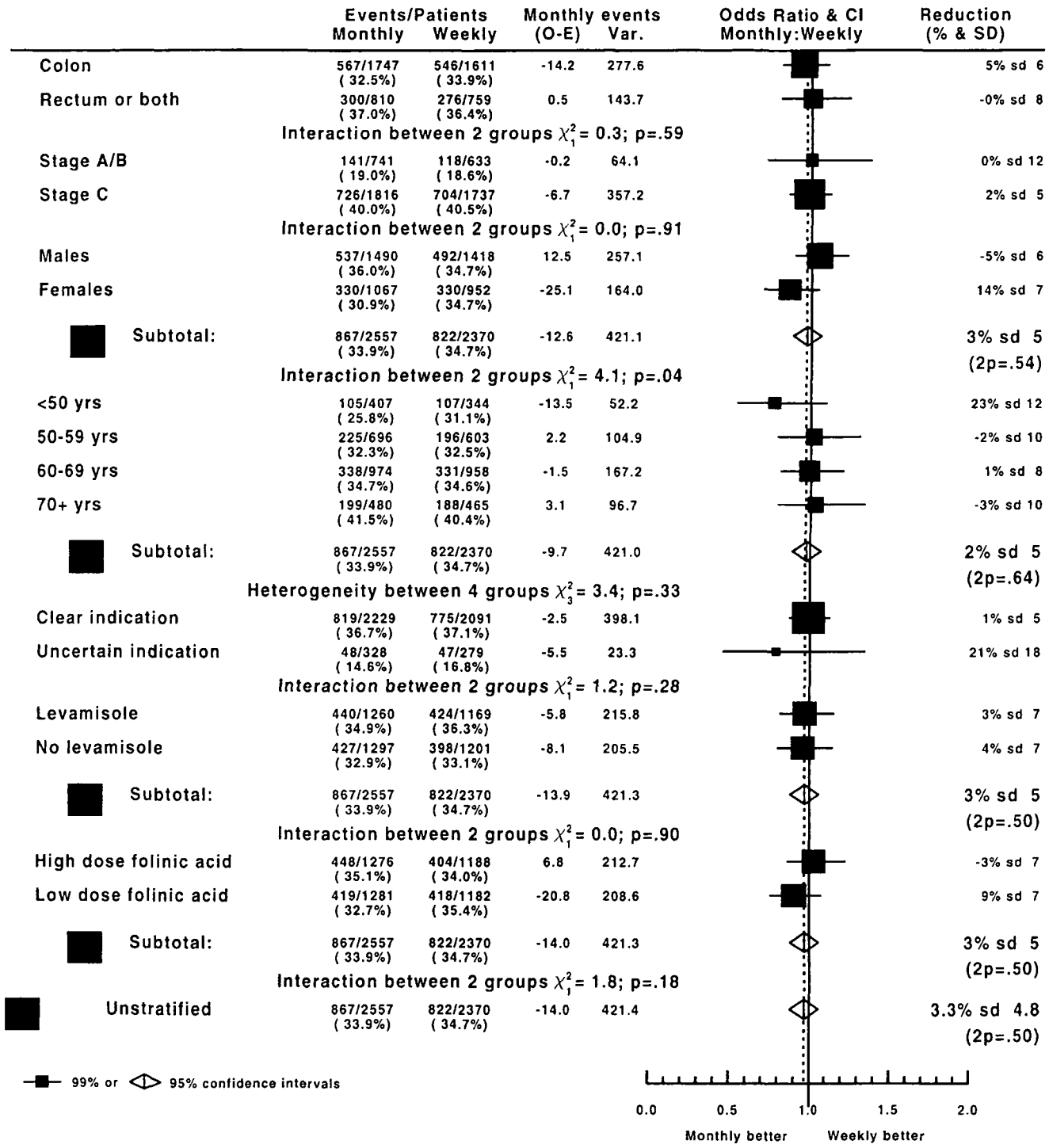

Figure 5 Effect of schedule on survival by tumour site, stage, sex, age and trial arm subgroups.

[23]. The antitumour activity increased significantly from 19% to 30%–35% when the two drugs were used concomitantly in multiple fractions per cycle rather than on a single day. However, fractionation changed the type of dose-limiting toxicity from haematologic and neurologic to gastrointestinal side effects. The different schedules did not differ significantly in the overall frequency of severe toxicities; however, these between trial comparisons may be biased by patient selection factors, and the authors of this study felt that recommending a certain schedule outside of controlled trials should be done cautiously [23]. The similar outcome with the once-weekly and four-weekly schedules in QUASAR shows their cautious interpretation was appropriate. The pharmacology of 5-FU is relatively well understood and there are some data to suggest that the molecular mechanism of 5-FU differs according to mode of administration, with a greater degree of DNA inhibition following bolus delivery and RNA inhibition with prolonged exposure. Therefore, not only might the method of drug administration influence its capacity to kill cycling cells, but also its fundamental mechanism of action.

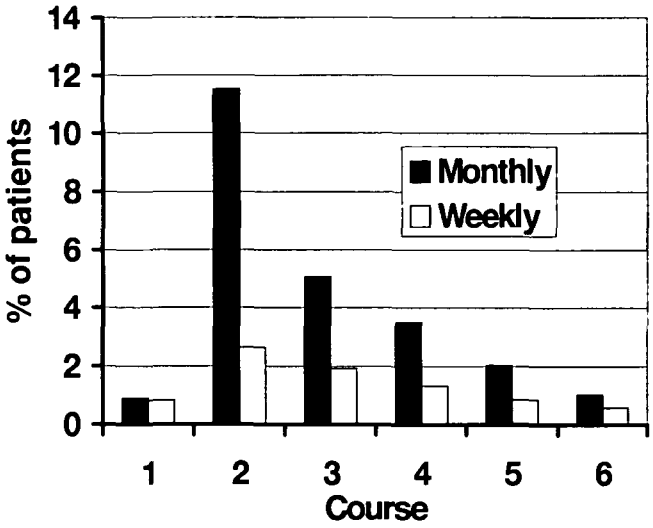

Figure 6. Timing of first dose reduction.

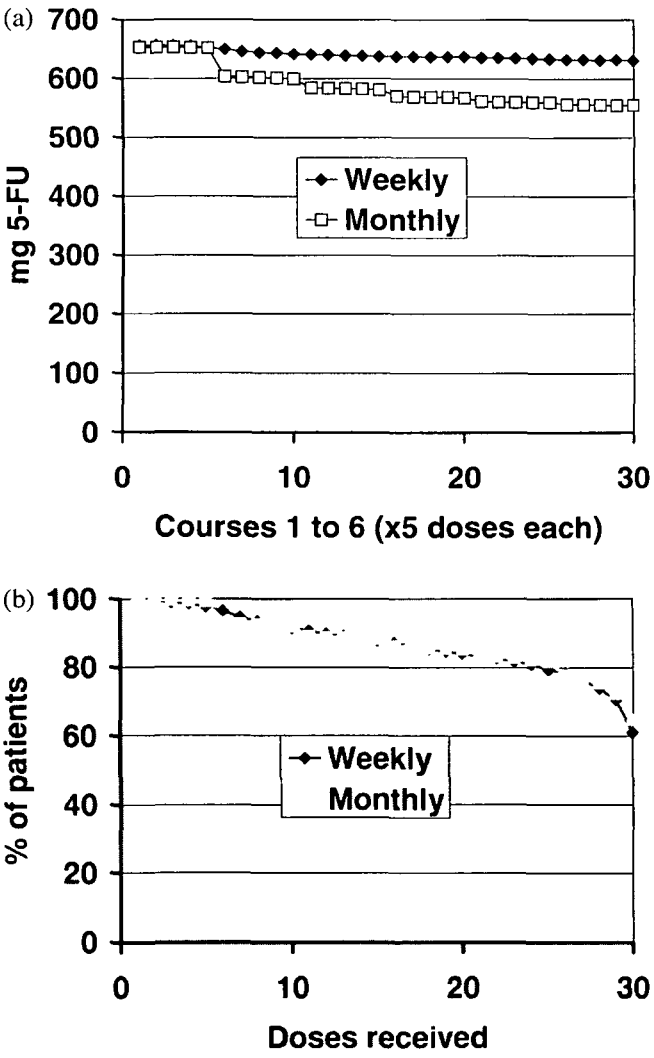

Figure 7. (a) Mean dose for courses received: (b) number of doses received.

One hypothesis worth considering is akin to Zeno's dialectic of the 'Tortoise and the Hare', in that the total amount of 5-FU delivered was higher for the weekly (tortoise) rather than the more dose intensive, rapidly delivered four-weekly (hare) schedule. This is related to the greatly increased incidence of toxicity driven dose reductions in the four-weekly schedule which resulted ultimately in a lower total delivered dose of 5-FU. Clearly the weekly dose of 5-FU in the QUASAR study is lower than those doses used in other weekly regimens [2–8], and it is likely that the dose of 5-FU could be increased, no doubt at the cost of increased toxicity. The lack of any apparent differences in efficacy between the two schedules raises the question of whether they were equally effective or equally ineffective. The latter seems unlikely as, although the absolute survival differences are moderate, the controlled trials of 5-FU–FA *versus* no chemotherapy collectively demonstrate a highly significant benefit. In addition the IMPACT trials group used the same regimen as the QUASAR high-dose regimen (5-FU 370 mg/m^2 and FA 200 mg/m^2 daily for five days every four weeks) and showed a significant survival benefit for this chemotherapy *versus* control.

One could conceive of a randomised trial comparing 5-FU 370 mg/m^2 and FA 20 mg/m^2 either by weekly or four-weekly schedules but with a dose escalation scheme added that would allow 15% increments in dose until grade 2 (assumed tolerable) toxicity was reached. This might be the truest way to determine the optimal dose of weekly 5-FU in combination with low dose folinic acid in a large population based trial, however it is inherently difficult to run trials with dose escalation steps unless there is a very committed clinical work force.

There is still a substantial debate about which group of colorectal cancer patients derive enough benefit from chemotherapy to justify its cost and toxicity. Of particular interest is the role of systemic adjuvant chemotherapy for Dukes' stage B and rectal cancer patients. The ongoing QUASAR 1 study should shed light on these issues.

Acknowledgements

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