Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis

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Summary

Background Treatment of advanced colorectal cancer has progressed substantially. However, improvements in response rates have not always translated into significant survival benefits. Doubts have therefore been raised about the usefulness of tumour response as a clinical endpoint.

Methods This meta-analysis was done on individual data from 3791 patients enrolled in 25 randomised trials of first-line treatment with standard bolus intravenous fluoropyrimidines versus experimental treatments (fluorouracil plus leucovorin, fluorouracil plus methotrexate, fluorouracil continuous infusion, or hepatic-arterial infusion of floxuridine). Analyses were by intention to treat.

Findings Compared with bolus fluoropyrimidines, experimental fluoropyrimidines led to significantly higher tumour response rates (454 responses among 2031 patients *vs* 209 among 1760; odds ratio 0·48 [95% CI 0·40–0·57], p<0·0001) and better survival (1808 deaths among 2031 *vs* 1580 among 1760; hazard ratio 0·90 [0·84–0·97], p=0·003). The survival benefits could be explained by the higher tumour response rates. However, a treatment that lowered the odds of failure to respond by 50% would be expected to decrease the odds of death by only 6%. In addition, less than half of the variability of the survival benefits in the 25 trials could be explained by the variability of the response benefits in these trials.

Interpretation These analyses confirm that an increase in tumour response rate translates into an increase in overall survival for patients with advanced colorectal cancer. However, in the context of individual trials, knowledge that a treatment has benefits on tumour response does not allow accurate prediction of the ultimate benefit on survival.

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Introduction

The 1996 recommendations of the Food and Drug Administration for accelerated approval of investigational cancer treatments state that for many cancer therapies use of objective evidence of tumour shrinkage is appropriate as a basis for approval, and that evidence of better survival or improved quality of life can be demonstrated later.[1] This statement marks a departure from the traditional requirements for new cancer treatments that benefits in survival or disease-free survival must be shown before market approval is granted.[2,3] Although the achievement of a complete response clearly has a major effect on prognosis in haematological malignant disease,[4–6] the relation between tumour response and survival duration in solid tumours is far less clear, even though the shrinkage of metastatic measurable masses has long been the cornerstone of the development of cytotoxic therapies.[7]

The relation between tumour response and survival is an important issue for patients with advanced colorectal cancer. Most of the therapeutic improvements for this cancer during the past 15 years have been documented in terms of tumour shrinkage. Using data from individual patients, we have confirmed in several meta-analyses that a tumour response could be achieved in about 10–15% of patients receiving bolus intravenous injections of fluoropyrimidines and that this response rate could be more than doubled with experimental regimens of fluoropyrimidine administration.[8–11] By contrast, the survival benefits of these experimental treatments were small, with median survival durations rarely exceeding 15 months. These observations raised doubts about the usefulness of tumour response as a clinical endpoint in assessment of new treatment approaches in this setting.

We report here our investigation of whether an improvement in tumour response rate leads to better survival in patients with advanced colorectal cancer. We studied the quantitative relation between the treatment effects on these two endpoints.

Methods

Data sources

We used individual data from 3791 patients enrolled in 25 previously reported randomised trials.[8–11] This dataset is the largest source of randomised data available in advanced colorectal cancer. All data were collected and checked by the Meta-Analysis Group in Cancer between 1990 and 1996 to confirm the benefits of experimental fluoropyrimidine treatments with fluorouracil or floxuridine (5-fluoro-2′-deoxyuridine) in advanced colorectal cancer. The principal investigators of all trials provided data for every patient, whether or not eligible and properly followed up. Items requested for every patient included baseline clinical characteristics (patient's identification, eligibility, date of random allocation, age, sex, performance status, primary tumour site, site of

metastases), treatment allocated by randomisation, tumour response,[12] duration of response (if applicable), date of death or last visit, survival status, and cause of death (if applicable). Four meta-analyses were done with these data. In all four meta-analyses, the comparison was between a control treatment and an experimental treatment. The control treatments, referred to as bolus fluoropyrimidines, were similar across the four meta-analyses and consisted of fluorouracil or floxuridine given as a bolus intravenous injection. The experimental treatments, referred to as experimental fluoropyrimidines, differed across the four meta-analyses: fluorouracil modulated by leucovorin;[8] fluorouracil modulated by methotrexate;[9] fluorouracil given by continuous infusion;[10] and hepatic-arterial infusion of floxuridine for patients with metastases confined to the liver.[11] Previous publications provide full details on the trials included, the treatments tested, the patients' characteristics, and the therapeutic results. For this paper, we concentrate on the relation between response and survival rather than on any specific treatment comparison.

Tumour response and survival

In all trials, complete response was defined as the disappearance of all detectable tumour and partial response as a decrease of 50% or more in the tumour surface area (sum of the products of the largest perpendicular diameters of all measurable disease), without appearance of new lesions. The minimum required response duration was 4 weeks in most of the trials. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in the tumour surface area, without new lesions. Progressive disease was defined as an increase of more than 25% in the tumour surface area or the appearance of any new lesion.[12] The best overall response of each patient was included in the analyses. The response rate was defined as the proportion of responders (complete or partial) among all patients. Survival time was taken from the day of random treatment allocation to the day of death irrespective of the cause of death.

Statistical methods

All analyses were based on data from individual patients and used a strict intention-to-treat approach. Hypothesis tests and estimation procedures were stratified for trial. To simplify graphical presentation, trials were grouped as suggested in the previous publications of the four meta-analyses.[8–11] The two-tailed significance level was set at 5%, and CIs were calculated with a 95% probability coverage.

We used the odds ratio to quantify treatment benefits in terms of tumour response. The response odds ratio was defined as the odds of failure to respond in the experimental group divided by the odds of failure to respond in the control group within each trial or category of trials. If r_1 is the response rate in the control group and r_2 the response rate in the experimental group, the response odds ratio is $(r_1\times[1\text{-}r_2])/(r_2\times[1\text{-}r_1])$, and the response odds reduction is equal to 1 minus the odds ratio. The statistical significance of odds reductions was assessed through the Mantel-Haenszel test.

We used the hazard ratio to quantify the treatment benefits in terms of survival. The survival hazard ratio was defined as the hazard rate in the experimental group divided by the hazard rate in the control group within each trial or category of trials. If h_1 is the hazard rate (or instantaneous risk of death) in the control group and h_2 the hazard rate in the experimental group, the survival hazard ratio is h_2/h_1, and the survival hazard reduction is equal to 1 minus the hazard ratio. Survival hazard ratios were estimated through life-table analyses based on individual survival times. The statistical significance of hazard reductions was assessed through the stratified

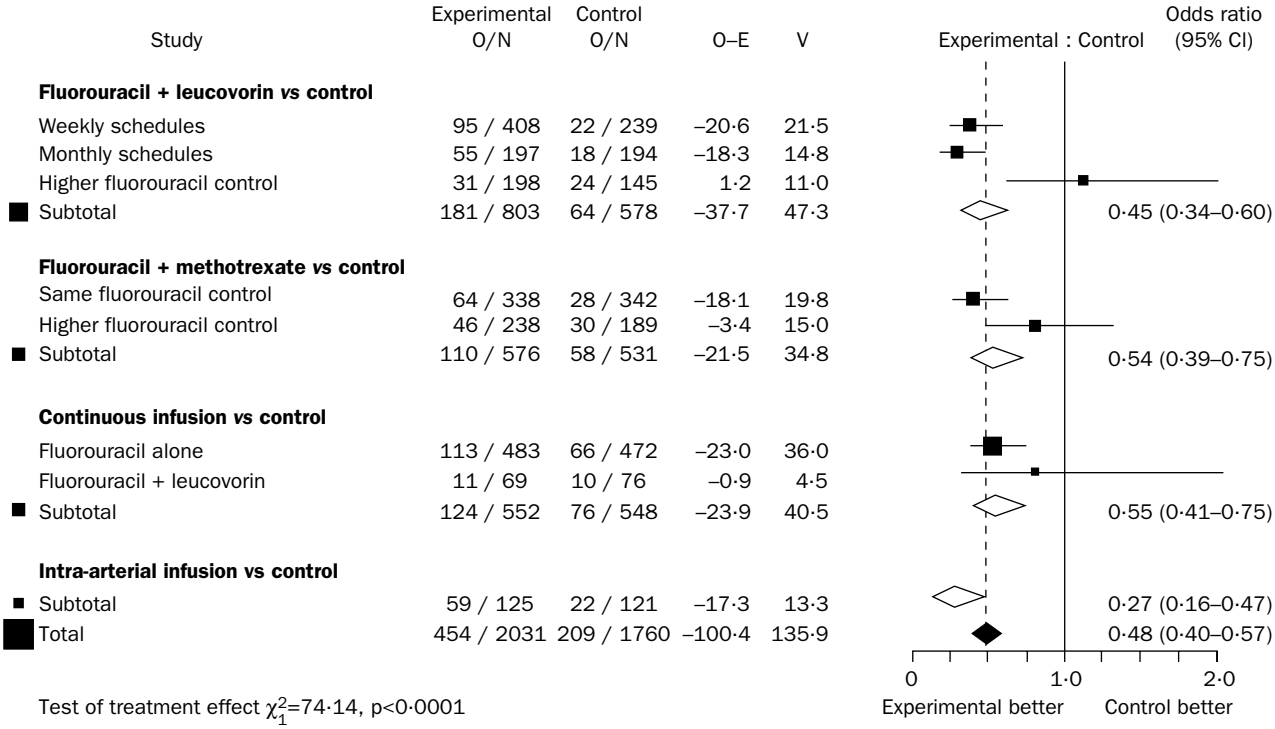

Figure 1: **Response odds ratios for experimental fluoropyrimidines over bolus fluoropyrimidines**
N=number of patients; O=observed number of responses; E=expected number of responses; V=variance of number of responses. Sums of N exceed numbers of patients because some trials contributed to more than one comparison.

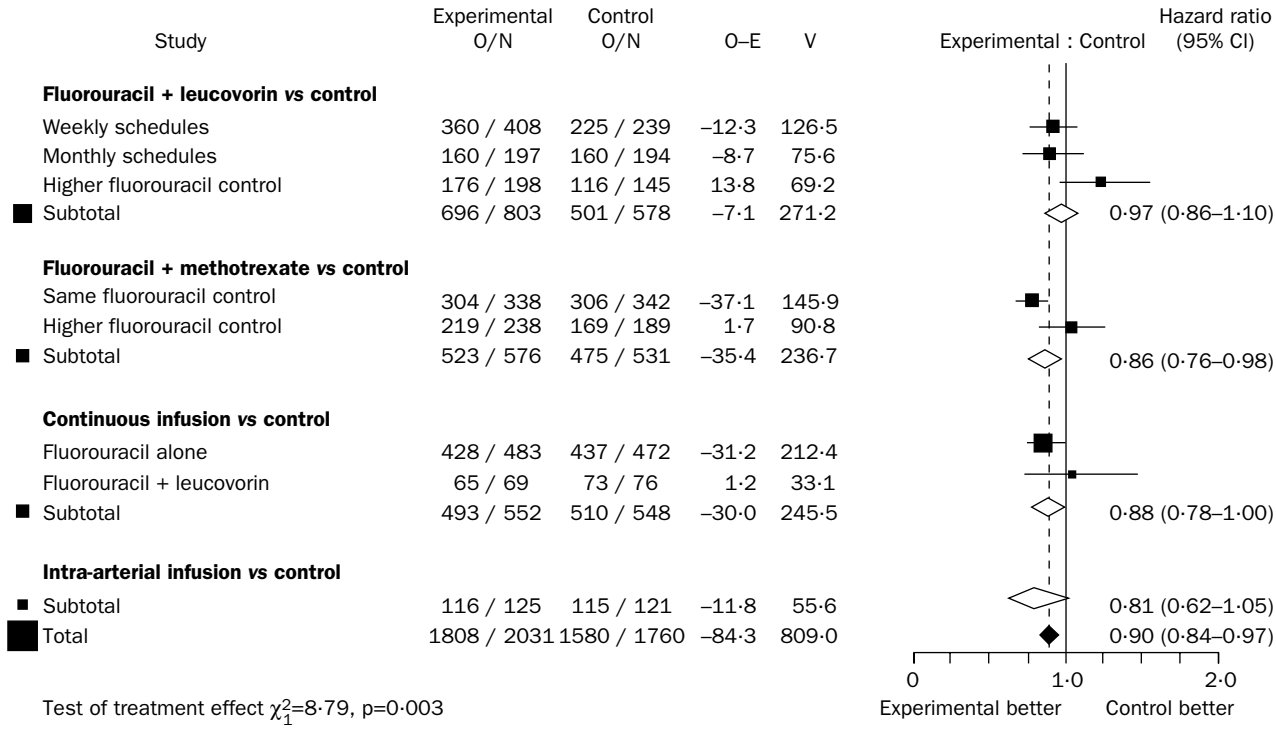

Figure 2: **Survival hazard ratios for experimental fluoropyrimidines over bolus fluoropyrimidines**
N=number of patients; O=number of deaths; E=expected number of deaths; V=variance of number of deaths. Sums of N exceed numbers of patients because some trials contributed to more than one comparison.

logrank test. To express hazard ratio in terms of median survival, we assumed that the survival times of patients with advanced colorectal cancer approximately follow a negative exponential distribution, in which case the hazard ratio is equal to m_1/m_2, where m_1 is the median survival in the control group and m_2 the median survival in the experimental group. Survival curves were estimated by the Kaplan-Meier method.

We analysed the prognostic effect of tumour response on survival by the landmark method to eliminate length-biased sampling from our analyses.[13] This method consists of ignoring responses that occur later than an arbitrary landmark time and deaths that occur before that time.[14]

We defined the relative effect as the ratio of the treatment effect on survival over the treatment effect on tumour response. We estimated relative effect as log (hazard ratio) divided by log (odds ratio).[15] In first approximation, relative effect is approximately equal to 1 minus the hazard ratio divided by 1 minus the odds ratio for response; hence, the relative effect estimates the ratio of the hazard reduction over the odds reduction. We fitted a weighted regression to predict treatment effects on survival (log hazard ratio) from treatment effects on response (log odds ratio).[16] The coefficient of determination of the regression line, R^2, gave the proportion of the variability in log hazard ratio that could be explained by the variability in log odds ratio.[17] Finally, we estimated the proportion of treatment benefits on survival that could be attributed to benefits on tumour response.[18,19]

Results

Effect of treatment on tumour response and survival

Although there was no treatment benefit in some categories of trials, the overall response odds ratio showed a highly significant benefit of experimental fluoropyrimidines over bolus fluoropyrimidines (odds ratio 0·48 [95% CI 0·40–0·57], p<0·0001; figure 1).

Effect of treatment on survival

The therapeutic benefits on survival were much less obvious than those on tumour response (figure 2), but the overall survival hazard ratio showed a significant benefit of experimental fluoropyrimidines over bolus fluoropyrimidines (hazard ratio 0·90 [0·84–0·97], p=0·003). The overall benefit of experimental fluoropyrimidines on survival is best shown by Kaplan-Meier survival curves (figure 3). There was a small but significant separation of the overall survival curves. The small treatment benefit was apparent in all subsets of patients, irrespective of performance status at entry to the trials (figure 3, table; p=0·002).

Effect of tumour response on survival

In advanced colorectal cancer, most tumour responses are observed after 2–6 months of therapy.[20] We used landmark times ranging from 1 month to 12 months and found that tumour response was a highly significant predictor of survival, irrespective of the landmark time chosen or adjustment for performance status (logrank p<0·0001).

We found no survival benefit from treatment in any of the tumour response categories (figure 3, table; p=0·42). The lack of survival benefit within distinct response categories suggests that the overall survival benefit in favour of experimental fluoropyrimidines was due to the higher tumour response rates obtained with experimental fluoropyrimidines than with bolus fluoropyrimidines, and not an antitumoral effect not captured by response. The proportion of the treatment benefit on survival that could be attributed to the improved response rates was estimated to be 0·95 (0·52–4·00).

Prediction of treatment effects on survival

The relative effect was estimated to be 0·12 (0·03–0·20). This estimate of relative effect indicates that the hazard reduction is about an eighth of the odds reduction—that is, if experimental fluoropyrimidines lowered the odds of failure to respond by 50%, they would be expected to lower the odds of death by only about 6% (2–10). Figure 4 shows the linear regression between treatment benefits on survival and on tumour response. The coefficient of determination of the regression line in figure 4 was 0·38 (0·09–0·68).

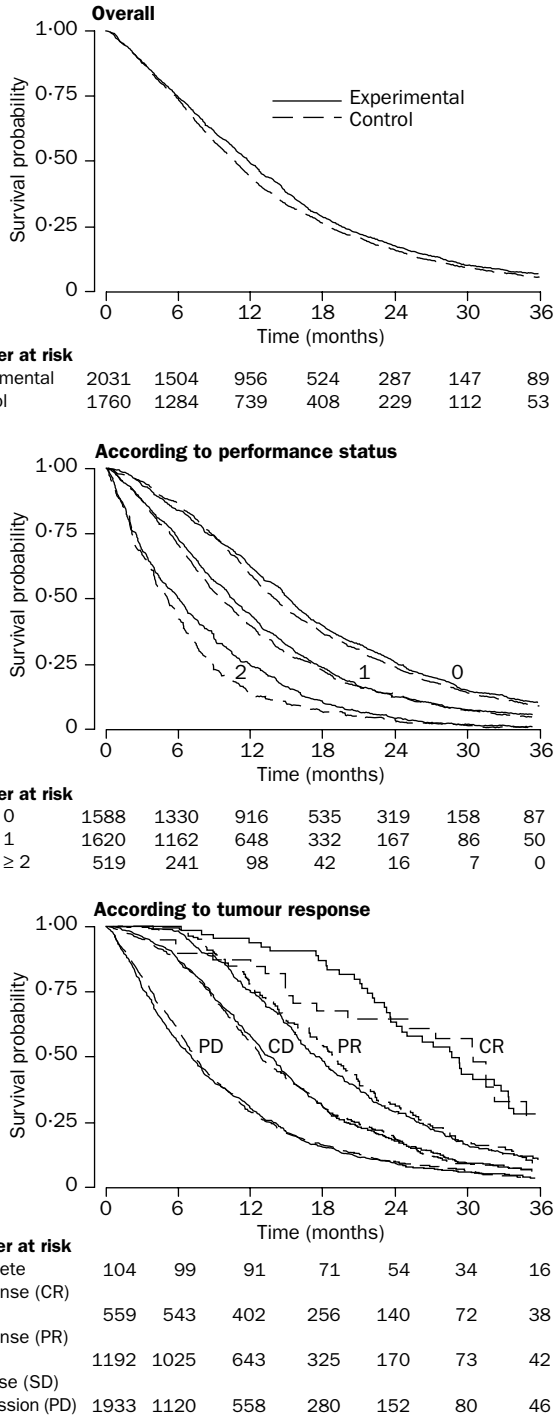

Figure 3: **Survival curves for patients randomly assigned experimental fluoropyrimidines or bolus fluoropyrimidines, overall and according to tumour response and performance status at trial entry**

See table for definition of performance status grades.

	Number of patients		Survival hazard ratio (95% CI)	p
	Experimental	Control		
Performance status*				
Grade 0	862 (43%)	726 (42%)	0·90 (0·80–1·00)	0·06
Grade 1	846 (43%)	774 (44%)	0·92 (0·83–1·02)	0·12
Grade ⩾2	281 (14%)	238 (14%)	0·81 (0·67–0·99)	0·04
Overall, stratified by performance status	1989	1738	0·89 (0·83–0·96)	0·002
Tumour response†				
Complete	64 (3%)	40 (2%)	0·84 (0·47–1·50)	0·54
Partial	390 (19%)	169 (10%)	1·02 (0·82–1·25)	0·89
Stable disease	604 (30%)	588 (33%)	0·95 (0·84–1·08)	0·45
Progressive disease	972 (48%)	961 (55%)	1·09 (0·99–1·20)	0·09
Overall, stratified by tumour response	2030	1758	1·03 (0·96–1·11)	0·42

Grade 0=able to carry out all normal activity without restriction; grade 1=restricted in strenuous activity but ambulatory and able to do light work; grade ⩾2=unable to carry out any work or confined to bed or chair.
*Unknown in 64 patients. †Unknown in three patients.

Survival hazard ratios for experimental over bolus fluoropyrimidines (control), according to initial performance status and tumour response to treatment

Discussion

These analyses confirmed that experimental fluoropyrimidines are superior to bolus fluoropyrimidines in terms of tumour response and identified a small but statistically significant overall survival benefit. The benefits of experimental fluoropyrimidines were much more impressive in terms of response rate than in terms of survival: overall, the response odds ratio was 0·48 whereas the survival hazard ratio was 0·90. These results underscore the importance of giving optimum first-line therapy to patients with advanced colorectal cancer, because treatments that induce higher response rates may ultimately be expected to prolong survival irrespective of second-line therapies and of the patient's initial performance status.

The relation between tumour response and survival has been inadequately approached in many studies by comparison of the survival of patients in whom a response was achieved with that of the other patients.[21] Such comparisons are biased because the patients who survive long enough to have an opportunity of responding to treatment have a predictably longer survival, on average, than the others even when treatment is wholly without effect on survival.[13,14] They are therefore misleading and cannot be regarded as proof of treatment benefit.[22] Our analyses, based on the landmark method to eliminate bias, showed that tumour response has a major prognostic effect on the survival of patients with advanced colorectal cancer,

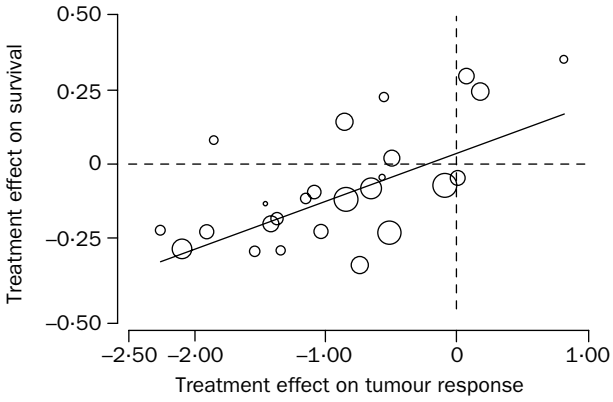

Figure 4: **Treatment effects on survival versus treatment effects on tumour response**

Each circle represents a trial, the area of which is proportional to the number of observations in the trial.

and that this effect is independent of other clinical factors such as the patient's performance status. These results accord with those reported in smaller series of patients with more detailed information on clinical prognostic factors.[20,23] Thus patients in whom a tumour response is achieved can be expected to derive a survival benefit from therapy.

Because we had individual data from large randomised series of patients, we could carry out further analyses to characterise the relation between tumour response and survival. We found evidence that the improvements in survival brought about by experimental fluoropyrimidines are mediated through improvements in tumour response, because the survival comparisons, after adjustment for response, were no longer significant. If experimental fluoropyrimidines had affected survival independently of tumour response, survival differences would have existed within each category of tumour response just as they exist, for example, within each category of performance status. Quantitatively, we estimated the proportion of the survival improvement that can be attributed to an improvement in tumour response as 0·95 (95% CI 0·52–4·00). This statistic is provided for comparison with existing reports on surrogate endpoints, but we have argued elsewhere that its use is not generally to be recommended.[24] The more relevant measure is the coefficient of determination of the regression line between the effects of treatment on response and the effects of treatment on survival (figure 4). This coefficient was 0·38, which means that less than half of the variability in the treatment effects on survival could be explained by treatment effects on response. In practice, such a low coefficient of determination implies that treatment effects on survival cannot be predicted reliably from treatment effects on response in individual clinical trials.

We quantified the relation between improvements in tumour response and survival through the relative effect.[16] We estimated that the relative effect (the ratio of the survival hazard reduction over the response odds reduction) was about one eighth (0·12). This relation is useful to predict likely survival benefits on the basis of response improvements observed in trials that are continuing or hoped for in future trials. For instance, let us suppose that patients treated with one of the modulated fluorouracil regimens in current use had a response rate of 20% (r_1=20%) and a median survival of 14 months (m_1=14 months).[8,9] If a new treatment were able to double the response rate (r_2=40%), the formulae given in the statistical methods indicate that this treatment could be expected to improve the median survival to about 16 months ($m_2 \approx 15{\cdot}7$ months). Even if the new treatment could triple the response rate (r_2=60%), the median survival would be unlikely to exceed 18 months ($m_2 \approx 17{\cdot}4$ months). Thus, only small survival benefits should be expected in patients with measurable metastatic colorectal cancer even with very large increases in the response rate.

Several factors may explain why survival improvements remain small in advanced colorectal cancer even when response rates are substantially improved. Patients who progress during treatment in clinical trials are withdrawn from the study protocol and receive second-line therapies that may themselves have a positive effect on overall survival. For instance, many of the patients assigned standard therapy in trials of hepatic-arterial infusion received the experimental therapy after standard therapy had failed to achieve a response.[11] Another reason for the small effect of tumour-response improvements on overall survival is that response rates remain small (under 30%) and short lived even in the most successful randomised trials, with few complete responses (less than 5%). Our models are based on trials in which only few complete tumour responses were observed (table). A much higher rate of complete responses is probably needed for the disease process to be significantly altered.

Our results have direct implications for the development of new drugs or combinations of drugs for the treatment of advanced colorectal cancer. They indicate that tumour response is a meaningful endpoint in testing new treatments for metastatic colorectal cancer because higher response rates predict longer survival, at least for the therapeutic comparisons included in our analyses. They provide some indirect justification for the policy of bringing to the adjuvant setting cytotoxic treatments that show superior response rates in advanced disease, even if these treatments do not improve survival in advanced disease. One example is leucovorin-modulated fluorouracil, which doubled the response rate compared with fluorouracil alone but had survival benefits too small to reach statistical significance in advanced disease.[8] As an adjuvant treatment for resected colon cancer, this treatment unequivocally improves survival compared with an untreated control group.[25–27] If several experimental drugs become simultaneously available for the treatment of colorectal cancer, a reasonable approach would be to screen these drugs primarily on the basis of their response rates, whether or not the drugs are ultimately expected to show survival benefits.[1] Endpoints other than survival, such as progression-free survival, merit interest because they are not affected by second-line therapy. If survival is deemed to be the primary endpoint in the development of a new treatment for advanced disease, to expect large benefits from a new treatment is unrealistic, especially if that new treatment is offered on a compassionate basis to the patients who do not respond to standard therapy. Because large differences in survival are unlikely even for treatments that have a major biological effect on the tumour, really large-scale randomised trials will then be needed. Even though our results cannot automatically be extrapolated to new treatments having different mechanisms of action from fluoropyrimidines, they may be useful in interpreting the outcomes of future trials in advanced colorectal cancer.

Contributors

Marc Buyse and Pascal Piedbois were responsible for conception and design of the study. All the investigators contributed to analysis and interpretation of the data. Pascal Piedbois, Robert Carlson, and Pierre Thirion provided clinical expertise. Marc Buyse, Tomasz Burzykowski, and Geert Molenberghs provided statistical expertise. The report was drafted, revised, and approved by all investigators.

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