

Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials

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Abstract

Objective To review the evidence from clinical trials of follow up of patients after curative resection for colorectal cancer.

Design Systematic review and meta-analysis of randomised controlled trials of intensive compared with control follow up.

Main outcome measures All cause mortality at five years (primary outcome). Rates of recurrence of intraluminal, local, and metastatic disease and metachronous (second colorectal primary) cancers (secondary outcomes).

Results Five trials, which included 1342 patients, met the inclusion criteria. Intensive follow up was associated with a reduction in all cause mortality (combined risk ratio 0.81, 95% confidence interval 0.70 to 0.94, $P=0.007$). The effect was most pronounced in the four extramural detection trials that used computed tomography and frequent measurements of serum carcinoembryonic antigen (risk ratio 0.73, 0.60 to 0.89, $P=0.002$). Intensive follow up was associated with significantly earlier detection of all recurrences (difference in means 8.5 months, 7.6 to 9.4 months, $P<0.001$) and an increased detection rate for isolated local recurrences (risk ratio 1.61, 1.12 to 2.32, $P=0.011$).

Conclusions Intensive follow up after curative resection for colorectal cancer improves survival. Large trials are required to identify which components of intensive follow up are most beneficial.

Introduction

Colorectal cancer is the second most common malignancy in Western societies and the second leading cause of death related to cancer.¹ At the time of initial diagnosis, about two thirds of patients undergo resection with curative intent, but 30-50% of these patients will relapse and die of their disease.² Some authors have postulated that intensive follow up would lead to early detection of recurrent disease or metachronous (second colorectal primary) tumours, or both, and thus improve survival, while others have questioned the need for follow up at all.³ This is reflected in current UK guidelines for the management of patients with colorectal cancer, which state that there is "no evidence" of survival benefit with intensive follow up⁴ or that it is "not worth while."⁵ There is currently wide variation in follow up.⁶⁻⁸ Among these many different protocols, the costs to health services are considerable and need to be justified with evidence.

We carried out a systematic review and meta-analysis of randomised clinical trials to determine whether there is any benefit of intensive follow up strategies after curative resection for colorectal cancer.

Methods

Search strategy—We searched Medline, Embase, CASCERLIT, and the Cochrane controlled trials register for relevant studies. We supplemented electronic searches by hand searching reference lists, reviews, and abstracts from meetings. National trial registers were also searched for unpublished trials. (Full details of search methods, inclusion and exclusion criteria, and data extraction methods are available on bmj.com)

Outcome measures—The primary outcome was all cause mortality at five years. Secondary outcomes were total number of recurrences, any type of local recurrences, isolated local recurrences, any hepatic metastases, isolated hepatic metastases, lung metastases, intraluminal recurrences, and metachronous (second colorectal primary) cancers.

Subgroup analysis—Different diagnostic tests were used during follow up in different trials. We performed a subgroup analysis based on the a priori hypothesis that the early detection of extramural recurrent disease (namely, local pelvic recurrences and solitary hepatic metastases), with investigations such as computed tomography or frequent measurements of serum carcinoembryonic antigen (at least every three months for two years and then every six months thereafter), or both, was more likely to be effective in improving survival related to cancer than strategies directed only at the detection of intraluminal disease (such as the use of colonoscopy).⁶

Results

Figure 1 shows the summary profile of the search. Five randomised controlled trials met our inclusion criteria.⁹⁻¹³ We also identified six ongoing trials or trials in preparation (details on bmj.com).

Study characteristics

The five included trials comprised 1342 participants: 666 assigned to intensive follow up and 676 assigned

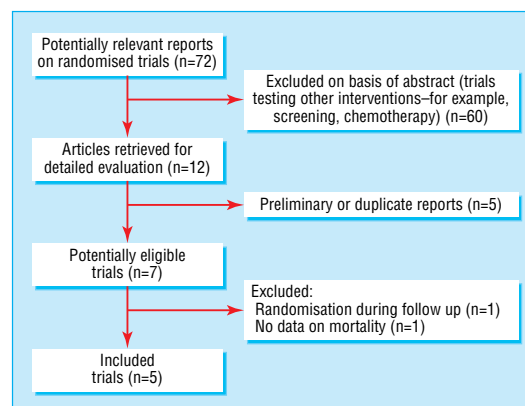


Fig 1 Summary of systematic review profile

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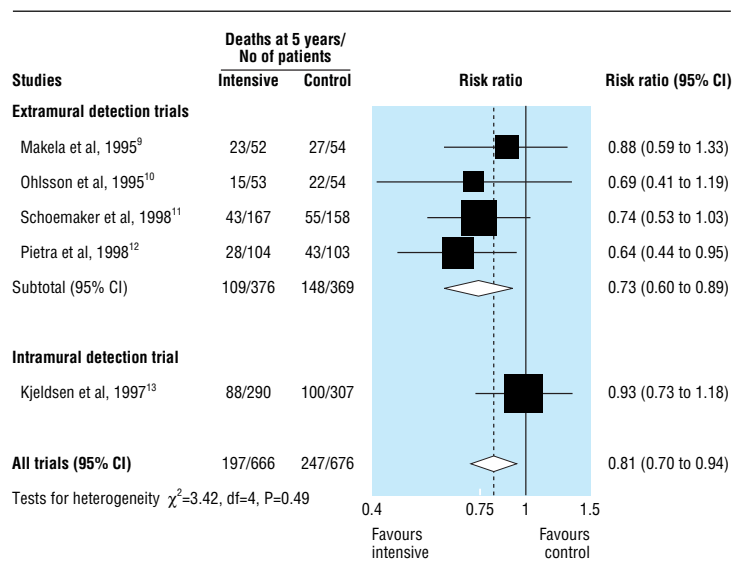


Fig 2 Pooled analysis with summary estimates (fixed effects method) for five year survival: data categorised into detection groups in accordance with a priori hypothesis (see methods)

to control. Details of the baseline characteristics of the participants enrolled in these trials are available on bmj.com

The tests and the frequency of their use varied considerably (table 1). No study directly compared specific tests, but in four trials computed tomography and frequent measurements of carcinoembryonic antigen were limited to the intensive arms.⁹⁻¹² We characterised these trials as the extramural detection group. The Danish study focused heavily on the increased detection of intraluminal disease and thus formed the intramural detection group.¹³

All cause mortality

Data on all cause mortality were available in all studies. Data on mortality related to cancer were available in only two studies.^{10, 13} At five years, 197 of 666 patients (30%) allocated to intensive follow up and 247 of 676 (37%) allocated to control groups had

died. By the fixed effects method, the combined risk ratio was 0.81 (95% confidence interval 0.70 to 0.94, $P=0.007$) in favour of intensive follow up (fig 2). Similar values for risk ratios were estimated by the random effects method. There was no significant heterogeneity.

The effect on mortality was most pronounced in the four extramural detection trials that used computed tomography and frequent measurements of serum carcinoembryonic antigen (combined risk ratio 0.73, 0.60 to 0.89, $P=0.002$). The five year mortality in the control groups ranged from 35% to 50%, which translates into an absolute reduction in mortality of 9% to 13% or a number needed to treat (the number of patients needed to prevent one death) of eight to 11. Little effect was seen in the Danish trial, which used only investigations to detect intramural disease (risk ratio 0.93, 0.73 to 1.18, $P=0.88$).

Recurrences, metastases, and metachronous cancers

There were no differences in rates of recurrence in all sites between the two groups: 212/666 (32%) for intensive versus 224/676 (33%) for control follow up. However, recurrences were detected 8.5 months (95% confidence interval 7.6 to 9.4 months) earlier with intensive follow up (table 2). Subgroup analysis in accordance with the a priori hypothesis revealed no distinct patterns.

The detection rates for all local recurrences and all hepatic and lung metastases were similar in the two groups. However, on the basis of data from three trials, intensive follow up was associated with a significant increase in detection of isolated local recurrences (15% v 9%: risk ratio 1.61, 1.12 to 2.32, $P=0.011$). Intensive follow up was also associated with a small non-significant increase in detection of hepatic metastases. Overall, rates of intraluminal recurrence and detection of metachronous cancer were low (3.2% and 1.3%, respectively), and there were no differences between follow up regimens.

Table 1 Detailed characteristics of surveillance programmes used in five randomised trials of intensive versus control follow up of patients after curative resection for colorectal cancer

Study	Intensive follow up	Control follow up
Makela et al, 1995 ⁹	Seen in clinic 3 monthly for first 2 years, then 6 monthly; physical examination, full blood count, faecal occult blood test, carcinoembryonic antigen levels, and chest x ray. Yearly colonoscopy. Sigmoidoscopy 3 monthly for rectal and sigmoid cancers. Ultrasonography of liver 6 monthly. Computed tomography yearly. All followed up to 5 years	Seen in clinic 3 monthly for first 2 years, then 6 monthly; physical examination, full blood count, faecal occult blood test, carcinoembryonic antigen levels, and chest x ray. Yearly barium enema. Rigid sigmoidoscopy 3 monthly for rectal cancers. All followed up to 5 years
Ohlsson et al, 1995 ¹⁰	Seen in clinic 3 monthly for the first 2 years, then 6 monthly; physical examination, rigid proctosigmoidoscopy, liver function tests, carcinoembryonic antigen levels, faecal occult blood test, chest x ray. Colonoscopy at 3, 15, 30, and 60 months, computed tomography after abdominoperineal resection at 3, 6, 12, 18, and 24 months. All followed up to 5 years	No systematic follow up. Patients were instructed to leave samples for faecal occult blood test testing every third month during the first 2 years and then every year. All accounted for to 5 years
Schoemaker et al, 1998 ¹¹	Seen in clinic 3 monthly for first 2 years, then 6 monthly for 5 years; physical examination, full blood count, liver function tests, and Haemocult II. Yearly chest x ray and computed tomography of liver. Yearly colonoscopy. Carcinoembryonic antigen measurements were performed but not used to trigger further examinations. 94% followed up to 5 years	Seen in clinic 3 monthly for first 2 years, then 6 monthly for 5 years; physical examination, full blood count, liver function tests, carcinoembryonic antigen levels, and Haemocult II. Carcinoembryonic antigen measurements were performed but not used to trigger further examinations. 95% followed up to 5 years
Pietra et al, 1998 ¹²	Seen in clinic 3 monthly for first 2 years, then 6 monthly for next 3 years, thereafter yearly; physical examination, ultrasonography of liver, carcinoembryonic antigen levels. Yearly colonoscopy, chest x ray, and computed tomography. All followed up to 5 years	Seen in clinic 6 monthly for first year, then yearly; physical examination, ultrasonography of liver, carcinoembryonic antigen levels. Yearly colonoscopy and chest x ray. All followed up to 5 years
Kjeldsen et al, 1997 ¹³	Physical examination, digital rectal examination, gynaecological examination, Haemocult-II, colonoscopy, chest x ray, full blood count, erythrocyte sedimentation rate, liver function tests, at 6 monthly in first 3 years, then 12 monthly for next 2 years, then 5 yearly. 79% followed up to 5 years	Physical examination, digital rectal examination, gynaecological examination, Haemocult-II, colonoscopy, chest x ray, full blood count, erythrocyte sedimentation rate, liver function tests, at 5 and 10 years. 73% followed up to 5 years

Table 2 Mean (SD) time (months) to first relapse in patients with colorectal cancer according to intensive or control follow up

	Intensive follow up	Control follow up	Differences in means (95% CI)
Makela et al, 1995 ⁹	10.0 (5.0)	15.0 (10.0)	-5.00 (-7.99 to -2.01)
Ohlsson et al, 1995 ¹⁰	20.4 (8.0)*	24.0 (7.0)*	-3.60 (-6.45 to -0.75)
Schoemaker et al, 1998 ¹¹	Not stated		
Pietra et al, 1998 ¹²	10.3 (2.7)	20.2 (6.1)	-9.90 (-11.19 to -8.61)
Subgroup†			-8.32 (-9.41 to -7.23)
Kjeldsen et al, 1997 ¹³	17.7 (8)§	26.5 (8.0)§	-8.80 (-10.25 to -7.35)
Pooled effect‡			-8.50 (-9.37 to -7.62)

*Estimated from ranges stated.

†Extramural detection trials.

‡Extramural and intramural detection trials.

§Estimated from geometric curves.

Discussion

The findings of this systematic review and meta-analysis of randomised controlled trials support the view that intensive follow up after curative resection for colorectal cancer improves survival at five years.

Survival benefit

This is the strongest evidence to date to show the beneficial effects of intensive follow up. Individual trials have been inconclusive, probably because of small sample sizes. Our analysis shows that using modern follow up regimens (including computed tomography or frequent measurements of serum carcinoembryonic antigen, or both) there was an absolute reduction in mortality of 9-13%. This improvement compares favourably with, for instance, the 5% benefit observed for adjuvant chemotherapy in Dukes' stage C disease^{4, 14} and is applicable to a wider range of clinical stages of colorectal cancer.¹⁵ In addition, the trials we included predated multidisciplinary approaches to the treatment of colorectal cancer, including the wider practice of hepatic resections for metastases, pelvic exenterations for recurrent pelvic disease, and the use of combined therapies for advanced disease. These approaches influence survival,³ and the potential survival benefits from intensive follow up may be even greater than those expressed in this analysis.¹⁵

Quality of trials

The quality of included studies should be considered in the interpretation of our findings. None of the trials reported adequate concealment of allocation nor comprehensive blinding of outcome assessment. Only two studies stated that randomisation was stratified for major prognostic factors. Despite these shortcomings, the strength of the present analysis is that it was limited to randomised controlled trials and that it supersedes previous meta-analyses, which were based on predominantly retrospective data.^{16, 17}

Mechanisms and future trials

Intensive follow up may improve survival in people with colorectal cancer because of earlier detection and treatment of recurrent disease. It may also be associated with non-specific factors, such as improved psychological wellbeing in patients. The detection rates in this analysis for all local recurrences and hepatic metastases were similar to those quoted in the literature,¹⁸⁻²⁰ but intensive follow up was associated with a reduced time to first relapse and increased detection of isolated local recurrences. This lends support to the former hypothesis. The importance of psychological factors remains unclear for patients with

colorectal cancer. The GIVIO study showed that increased psychological support influences survival in patients with breast cancer but not in those with colorectal cancer.²¹ On the other hand, increased psychological support may influence outcome in particular groups of patients with gastrointestinal cancer.²²

Many clinicians favour colonoscopic surveillance (intramural detection) over investigations aimed at the detection of extramural recurrences.^{6, 8} Our findings show that this is not justified. As seen in previous studies^{23, 24} we found that intraluminal recurrences and metachronous cancers were uncommon, irrespective of the intensity of follow up. Therefore, intensive efforts directed at the detection of intraluminal disease are probably of low benefit. We could not address the impact on outcome of intensive follow up through the detection of adenomas, known precursors of malignancy, but increasingly it is recognised that screening for adenomas is most beneficial in those aged 55-65 years.²⁵ For many patients with colorectal cancer this opportunity may have passed.

We could not evaluate the efficacy of individual investigations used in colorectal cancer surveillance. This review represents a pragmatic evaluation of two broad strategies of surveillance. Future large multi-centre trials should use a factorial design to allow separation of the effects of different tests performed during

What is already known on this topic

There is a lack of direct evidence that intensive follow up after initial curative treatment for colorectal cancer leads to increased survival

Guidelines are inconclusive and clinical practice varies widely

What this study adds

The cumulative analysis of available data supports the view that intensive follow up after curative resection for colorectal cancer improves survival

If computed tomography and frequent measurements of serum carcinoembryonic antigen are used during follow up mortality related to cancer is reduced by 9-13%

This survival benefit is partly attributable to the earlier detection of all recurrences, particularly the increased detection of isolated recurrent disease

follow up. Application of the principles of intensive follow up in this common cancer has potentially important financial and resource implications for health services. Although estimation of the cost per life years gained is beyond the scope of this paper, the present study should serve as a basis for economic modelling in future trials. Finally, while wide variation in follow up persists in clinical practice, we believe that clinical guidelines should be revised.

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Cross sectional survey of parents' experience and views of the postmortem examination

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Abstract

Objective To describe parents' experience and views of the postmortem examination after the loss of a baby.

Design Cross sectional survey.

Setting Hospital with a dedicated bereavement counselling service, Newcastle upon Tyne.

Participants 258 women who had attended a bereavement counselling service at the Royal Victoria Infirmary, Newcastle upon Tyne, on at least one occasion after losing a baby during pregnancy or infancy, between October 1996 and October 2000.

Method Self completion postal questionnaire incorporating fixed choice and open ended questions.

Main outcome measures Number of respondents who were asked if they would agree to a postmortem examination of their baby, and number who agreed to a postmortem examination; reasons for agreeing and not agreeing to a postmortem examination; quality of explanation received; number who regretted their decision to give or withhold consent for a postmortem examination.

Results 166 (64%) respondents completed the questionnaire. Of these, 148 (89%) had been asked to agree to a postmortem examination on their baby and 120/148 of these respondents (81%) agreed, most of whom recognised benefits resulting from the examination. 101/117 (86%) respondents believed the findings had been explained appropriately. Nine (7%) of the 120 respondents who had agreed to a postmortem examination regretted their decision. Of the respondents who refused an examination, four (14%) had regrets about their decision.

Discussion Parents viewed the postmortem examination as a useful and necessary tool in helping to discover the reasons why their baby had died. Simplifying the language used to explain findings may further raise parents' understanding of the value of the postmortem examination and ensure that they are satisfied with it. Medical staff involved in consent for postmortem examinations should be fully trained in how to ask for parental consent, the postmortem examination procedure, and how to explain the findings.



Comments from parents in this study can be found on bmj.com