

# Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer

Andrew G Renehan, Sarah T O'Dwyer, David K Whynes

## Abstract

**Objective** To determine the cost effectiveness of intensive follow up compared with conventional follow up in patients with colorectal cancer.

**Design** Incremental cost effectiveness analysis recognising differences in follow up strategies, based on effectiveness data from a meta-analysis of five randomised trials.

**Setting** United Kingdom.

**Main outcome measures** Taking a health service perspective, estimated incremental costs effectiveness ratios for each life year gained for five trials and four trials designed for early detection of extramural recurrences (targeted surveillance).

**Results** Based on five year follow up, the numbers of life years gained by intensive follow up were 0.73 for the five trial model and 0.82 for the four trial model. For the five trials, the adjusted net (extra) cost for each patient was £2479 (€3550; \$4288) and for each life year gained was £3402, substantially lower than the current threshold of NHS cost acceptability (£30 000). The corresponding values for the four trial model were £2529 and £3077, suggesting that targeted surveillance is more cost effective. The main predictor of incremental cost effectiveness ratios was surveillance costs rather than treatment costs. Judged against the NHS threshold of cost acceptability, the predicted incremental cost threshold was ninefold and the effectiveness threshold was 3%.

**Conclusions** Based on the available data and current costs, intensive follow up after curative resection for colorectal cancer is economically justified and should be normal practice. There is a continuing need to evaluate the efficacy of specific surveillance tools: this study forms the basis for economic evaluations in such trials.

## Introduction

More than 35 000 new cases of colorectal cancer occur in the United Kingdom each year, representing a major disease burden on health services.<sup>1 2</sup> Recently, the present authors and a Cochrane review group independently reported two meta-analyses of all randomised trials of follow up strategies for patients treated for colorectal cancer and showed a significant improvement in all cause mortality in patients followed intensively.<sup>3 4</sup> A further randomised trial has since been published supporting these findings.<sup>5</sup> We aimed to determine the cost effectiveness of intensive follow up compared with conventional follow up in patients treated for colorectal cancer.

## Methods

We performed a cost effectiveness analysis based on the results of our previous meta-analysis of five randomised trials (1342 patients; five trial model),

which showed a significant reduction in all cause mortality at five years (absolute reduction 7%) in patients followed intensively.<sup>3 6-10</sup> Our second analysis was based on effectiveness data from four trials (745 patients; four trial model), where surveillance tools were targeted at the detection of extraluminal recurrences and where improvement in survival was more pronounced (absolute reduction 9%).<sup>6-9</sup>

## Costs

We adopted a health service perspective and calculated patient specific costs related to five year follow up strategies for colorectal cancer (intensive compared with conventional) by estimating costs for surveillance and treatment of recurrences. Costs were based on 2002 UK prices and included direct, indirect, and overhead costs. We used a "bottom-up" approach, rounding costs upward and seeking to be as inclusive as possible in estimates. Sources included the Department of Health reference costs and related cost effectiveness studies (see [bmj.com](http://bmj.com)).<sup>11-13</sup>

Because follow up regimens and surveillance tests varied considerably between and within trials, it was necessary for us to estimate costs separately for each trial and then to calculate the costs for each patient.<sup>3</sup> Costs included clinical follow up visits (administration, clinical examination, consumables), laboratory tests (reagents, consumables, staff, service costs, processing, and reporting), endoscopic investigations and polypectomy (administration, drugs, consumables, staff, sterilisation, annual equivalent costs for equipment), and radiology (staff, consumables, service costs, processing and reporting, annual equivalent costs for equipment; table).<sup>14 15</sup>

In calculating treatment costs, we incorporated into our model three possible outcomes after the detection of recurrences: inoperable disease requiring symptomatic treatment and palliative care, salvage with cure, and salvage with subsequent failure and palliative care (see figure on [bmj.com](http://bmj.com)). Treatment costs were then estimated for salvage and palliative treatments for local, hepatic, and other site recurrences. Salvage costs included surgery with average hospital stay, peri-operative investigations, high dependency care, blood transfusion, drug usage, stoma care, and care by a district nurse (see [bmj.com](http://bmj.com)). A further 35% was added to salvage therapy costs (intensive and conventional follow up) to account for high rates of complications and reoperations associated with these types of treatments.<sup>16 17</sup> Palliation costs included palliative surgery and stoma care, palliative radiotherapy, palliative medical care, and cancer care in the community. Chemotherapy regimens were not used in any trial.

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BMJ 2004;328:81-4



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Unit cost estimate for surveillance and treatment of recurrent colorectal cancer

Costs	Mean cost (£)	Maximum cost (£)
<b>Surveillance</b>		
Physical examination	58.80	281.80
Laboratory tests:		
Full blood count	9.30	18.30
Erythrocyte sedimentation rate	9.30	18.30
Liver function test	9.30	23.30
Carcinoembryonic antigen	9.30	23.30
Faecal occult blood test	14.00	76.00
Endoscopy:		
Rigid sigmoidoscopy	98.80	321.80
Flexible sigmoidoscopy (examination only)	156.41	578.37
Flexible sigmoidoscopy with biopsy or polypectomy*		
Colonoscopy (examination only)	229.15	545.92
Colonoscopy with biopsy or polypectomy†		
Imaging:		
Chest radiography	22.40	148.40
Barium enema radiography	138.40	610.40
Liver ultrasonography	104.40	264.40
Abdominal or pelvic computed tomography	171.20	777.20
<b>Treatment</b>		
Intensive follow up:		
Local salvage therapy	11 258	32 108
Local palliative therapy	4 102	14 284
Hepatic salvage therapy	9 513	2 541
Hepatic palliative therapy	1 288	6 075
Control follow up:		
Local salvage therapy	11 630	33 915
Local palliative therapy	4 377	15 622
Hepatic salvage therapy	9 885	27 348
Hepatic palliative therapy	1 563	7 413

£1 (€1.4; \$1.7).

Estimates include direct, indirect, and overhead costs based on 2002 prices. Sources of cost estimates from Department of Health reference costs, Gilbert et al,<sup>12</sup> multicentre aneurysm screening study,<sup>13</sup> and in-house financial department (see bmj.com).

\*Modelled that 21% of patients may have distal colonic polyps<sup>14</sup>; probably an overestimate but included as part of "bottom-up" approach to estimations.

†Modelled that 27% of patients undergoing surveillance colonoscopy will require biopsy or polypectomy (control data from Sandler et al<sup>15</sup>).

### Outcome measures

The primary outcome was the extra cost per unit of outcome obtained in comparing one treatment with another (incremental cost effectiveness ratio) for each change in life year for intensive follow up compared with conventional follow up.<sup>18</sup> We calculated life years lost and gained for each trial using average life expectancies for the UK population.<sup>19</sup> The probability that intensive follow up is cost effective depends on how much the NHS is willing to pay for each life year gained—the value of £30 000 (€42 968; \$51 888) was used (referred to as NHS cost acceptability), reflecting the currently perceived threshold in the United Kingdom.<sup>20</sup> In the base case analysis, we discounted benefit effects at 1.5% and costs at 6.0%.<sup>21</sup>

### Sensitivity analyses

We undertook several sensitivity analyses to illustrate the impact of the principal aspects of uncertainty on the estimate of cost effectiveness. These included changes to surveillance and treatment costs, and changes to discount rates.

Using the NHS cost acceptability of £30 000 as reference, we calculated the incremental increase in costs required to increase the incremental cost effectiveness ratio to the limit of NHS cost acceptability (incremental cost threshold) by simultaneous incremental increases in surveillance and treatment costs for both

intensive and conventional follow up. We also calculated the lowest level of effectiveness—absolute reduction in mortality—required to increase the incremental cost effectiveness ratio to the limit of NHS cost acceptability (threshold of effectiveness). The threshold of effectiveness was calculated by altering differences in benefit between follow up strategies by amounts equivalent to 1% change in mortality (see bmj.com).

### Results

The figure shows the Forest plot for all cause mortality with absolute reductions in mortality, together with the calculated life years lost and gained for each patient for each study and associated cost effectiveness ratios. For the five trial model, the lost and gained calculations favoured intensive follow up by 0.73 life years gained for each patient, increasing to 0.82 life years gained for each patient for the four trial model, consistent with the observations from our previous meta-analysis.<sup>3</sup> In the five trial model, the adjusted net (extra) cost for each patient was £2479 and for each life year gained was £3402, substantially lower than the current NHS threshold of cost acceptability. The corresponding values for the four trial model were £2529 and £3077, suggesting that targeted surveillance is more cost effective.

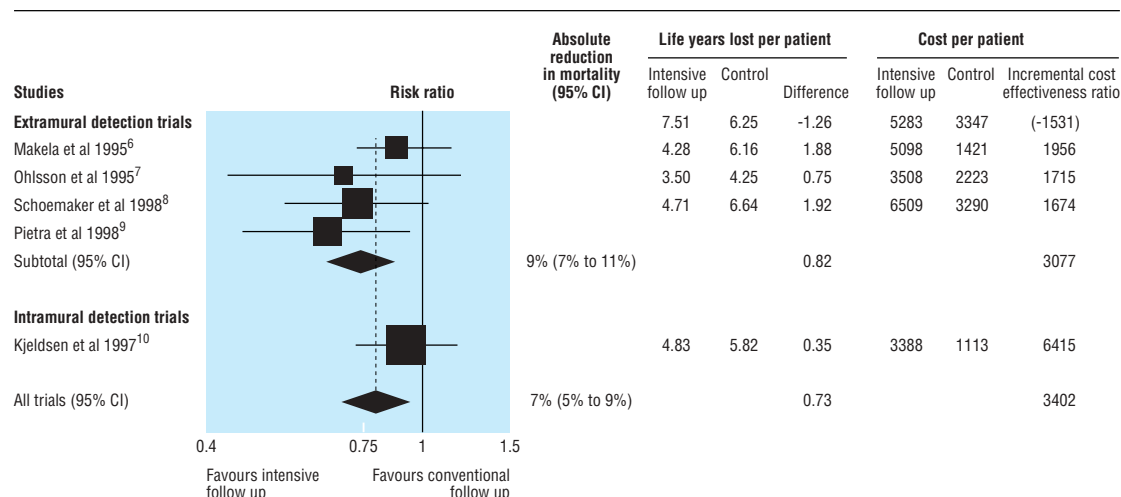
Worst case scenario analyses showed that substituting with maximum surveillance costs produced greater increases in cost effectiveness ratios compared with substituting with maximum treatment costs, indicating that surveillance cost is the most important determinant of cost effectiveness. All cost effectiveness ratios for maximum cost estimates fell within the NHS acceptability threshold on cost. The incremental cost threshold was near ninefold for both the five trial (£30 620) and four trial (£27 695) models. For both models the threshold of cost effectiveness was an absolute reduction in mortality of 3%.

### Discussion

Intensive follow up after curative resection for colorectal cancer improves all cause mortality at five years and has a cost effectiveness ratio well within the NHS acceptability of willingness to pay for each life year gained. This economic analysis, based on effectiveness data from a previous meta-analysis, provides firm estimates of the cost of intensive follow up. The data also suggest that targeted follow up improves cost effectiveness.

Previous studies have examined economic issues related to follow up after treatment for colorectal cancer,<sup>22–27</sup> but predated the effectiveness data provided by the two recently published meta-analyses.<sup>3, 4</sup> Previous studies have examined economic issues related to follow up after treatment for colorectal cancer but predated the effectiveness data provided by the two fore-mentioned meta-analyses.<sup>22–27</sup> The present analysis is strengthened by the inclusion of a comprehensive search to include many aspects of cost estimates (a "bottom-up" approach) and sensitivity analyses at several levels.

Our study emphasises a further aspect, that around equal proportions (one third) of patients with colorectal cancer develop recurrences, irrespective of



Forest plot of randomised trials. Pooled analysis with summary estimates (Mantel-Haenszel fixed effects method) are for all cause mortality (adapted from Renehan et al 2002<sup>3</sup>). Data are categorised into extramural and intramural detection groups. Positive difference indicates time gained (improved survival). See [bmj.com](http://bmj.com) for calculation of estimates. Incremental cost effectiveness ratio=[costs for each patient for intensive follow up minus control follow up]/[discounted life years either gained or lost]

follow up strategy. After detection of recurrence, palliative therapy (more common in control patients) is not without expense and partially offsets the costs of salvage therapy (more common in patients followed intensively).

The first limitation of our study was the clinical heterogeneity of follow up regimens among the five trials.<sup>3</sup> No study directly compared specific tests, so it was not possible to evaluate the cost effectiveness of specific surveillance tools. A second limitation was the lack of quality of life data. The third limitation was the absence of individual patient data, such that we had to make assumptions about survival and recurrence patterns. These assumptions, however, held firm, as shown by the sensitivity analysis. The fourth limitation was that the included trials were conducted over a decade ago and did not include aspects of contemporary practice (for example, multidisciplinary management) that could impact on costs or effectiveness. The final limitation is that we were unable to compare intensive follow up with no follow up (zero surveillance costs), although in modern practice the acceptability of a no follow up strategy is questionable.<sup>28</sup>

The strategy of intensive follow up after curative resection for colorectal cancer is economically justified and should be normal practice. As a screening type health strategy, intensive follow up of patients with colorectal cancer compares favourably with screening for breast and colorectal cancers and for abdominal aortic aneurysms.<sup>13 29 30</sup> Moreover, compared with population screening, these patients are self defined, well motivated, and compliant.<sup>31</sup>

Large randomised trials are needed to evaluate the efficacy of specific surveillance tools.<sup>3 28</sup> These studies must include cost effectiveness analyses and quality of life assessments, in addition to other issues that were beyond the scope of our analysis. Firstly, costs beyond five years after initial treatment need to be considered. Secondly, our included trials predated the widespread use of chemotherapy for advanced colorectal cancer or as an adjunct to salvage reoperation, approaches that may improve survival.<sup>32</sup> Thirdly, our analysis treated

### What is already known on this topic

Intensive follow up after curative resection for colorectal cancer improves survival (absolute effects 7-9%)

The cost effectiveness of intensive surveillance is uncertain

### What this study adds

The number of years gained through intensive surveillance over five years is 0.73 to 0.82 for each patient

The adjusted net cost for each patient was £2479 and for each life year gained was £3402, substantially lower than the NHS threshold of cost acceptability (£30 000)

Corresponding values for four trials using targeted surveillance were £2529 and £3077, suggesting that this approach may be more expensive but improves cost effectiveness

local, hepatic, and other site recurrences as mutually exclusive events. In practice there is overlap, which will tend to attenuate costs. Fourthly, we did not address societal perspectives, such as travel and time off work, which could be important determinants of compliance in cancer surveillance.<sup>33</sup> Fifthly, it was not possible to estimate capital costs for additional laboratory and clinical capacity. Finally, we did not consider the benefits of intensive follow up to factors other than salvage for recurrent disease—for example, psychosocial benefits or improved treatment of coincidental disease.

Funding: None.

Contributors: See [bmj.com](http://bmj.com)

Competing interests: None declared.

Ethical approval: Not required.

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(Accepted 16 October 2003)

## Is there a familial link between Down's syndrome and neural tube defects? Population and familial survey

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### Abstract

**Objective** To verify whether Down's syndrome and neural tube defects arise more often in the same family than expected by chance.

**Design** Population and familial survey.

**Setting** Network of maternity hospitals in the Latin American collaborative study of congenital malformations (ECLAMC) in Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, and Venezuela between 1982 and 2000.

**Probands** 2421 cases of neural tube defects, 952 of hydrocephalus, and 3095 of Down's syndrome registered from a total of 1 583 838 live births and stillbirths.

**Main outcome measures** Observed number of cases of Down's syndrome among siblings of probands with a neural tube defect or hydrocephalus and number expected on the basis of maternal age; observed number of cases of neural tube defects or hydrocephalus among siblings of probands with Down's syndrome and number expected according to the prevalence in the same population.

**Results** Five cases of Down's syndrome occurred among 5404 pregnancies previous to a case of neural tube defect or hydrocephalus, compared with 5.13 expected after adjustment by maternal age. Twelve cases of neural tube defect or hydrocephalus occurred among 8066 pregnancies previous to a case of Down's syndrome, compared with 17.18 expected on the basis of the birth prevalence for neural tube defects plus hydrocephalus in the same population.

**Conclusion** No association occurred between families at risk of neural tube defects and those at risk of Down's syndrome.

### Introduction

An association between abnormal intake or metabolism of folate and neural tube defects has been proved.<sup>1-3</sup> At the molecular level, the 677C→T (alanine to valine) polymorphism in the gene encoding the

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*BMJ* 2004;328:84-7



This article was posted on [bmj.com](http://bmj.com) on 8 December 2003:  
<http://bmj.com/cgi/doi/10.1136/bmj.37945.610914.EE>