Papers

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

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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.[1 2] At initial presentation, around two thirds of patients undergo resection with curative intent, and most enter some type of long term follow up.[3] The rationale behind this is threefold: psychological support, facilitation of audit, and the early detection and treatment of recurrent disease, with potential improvement in survival.[4] The merits of early detection and treatment of recurrent disease have been vigorously debated. 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.[5 6] A further ran-domised trial has since been published supporting these findings.[7] These data are the first direct evidence that intensive follow up improves survival.

Against the emerging evidence of the effectiveness of intensive follow up, follow up practice varies widely worldwide and, among these many different protocols, the costs to health services are considerable.[8–10] We compared the cost effectiveness of intensive follow up with conventional follow up in patients treated for colorectal cancer.

Methods

Our cost effectiveness analysis was 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.[5 11–15] Our second analysis was based on effectiveness data from four trials (four trial model), where surveillance tools were targeted at detecting of extraluminal recurrences and where improvement in survival was more pronounced (absolute reduction 9%).[11–14]

Costs

We adopted a health service perspective and calculated patient specific costs related to five year follow up strategies for colorectal cancer (intensive follow up compared with conventional follow up) 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).[16–18] The Department of Health reference costs are aggregate direct costs for trust hospitals nationwide and present costs as mean, minimum, and maximum values.

Because follow up regimens and surveillance tests varied considerably between and within trials, we estimated costs separately for each trial and then calculated the costs for each patient.[5] 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,

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Table 1 Unit cost estimate for surveillance and treatment of recurrent colorectal cancer

Costs	Mean cost (£)	Maximum cost (£)
Surveillance		
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)		
Flexible sigmoidoscopy with biopsy or polypectomy*	156.41	578.37
Colonoscopy (examination only)		
Colonoscopy with biopsy or polypectomy†	229.15	545.92
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
Treatment		
Intensive follow up:		
Local salvage therapy	11 258	32 108
Local palliative therapy	4102	14 284
Hepatic salvage therapy	9513	2 541
Hepatic palliative therapy	1288	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,[17] multicentre aneurysm screening study,[18] and in-house financial department (see bmj.com).

*Modelled that 21% of patients may have distal colonic polyps[19]; 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[20]).

processing and reporting, annual equivalent costs for equipment; table 1).[19 20] As follow up rates were high for all trials, we modelled full attendance for each prescribed examination and surveillance investigation until five years or death.[5] We modelled for additional investigations (namely computed tomography) owing to a 15% false positive rate when testing for serum carcinoembryonic antigen.[21]

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). For patients followed conventionally, we modelled that the initial assessment of recurrent disease (the decision between palliation and salvage) was based on off-trial investigations, whereas the assessment of recurrent disease was encompassed by protocol investigations in patients followed intensively.[14] 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, perioperative investigations, high dependency care, blood transfusion, drug usage, stoma care, and care by a district nurse (see 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.[22 23] 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.

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.[24] We calculated life years lost and gained for each trial using average life expectancies for the UK population and taking into account the proportions of males and females, the mean ages at initial treatment, and the number of deaths.[25] Costs were calculated for each trial and then expressed as costs for each patient and aggregated. 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.[26]

Censoring and discounting
In the absence of individual patient data, we modelled the distribution of censored events (deaths) by constant numbers for each three month period. In practice, surveillance would generally be discontinued (censored) after recurrence, such that this model tends to overestimate surveillance costs. In the base case analysis, we discounted benefit effects at 1.5% and costs at 6.0%.[27]
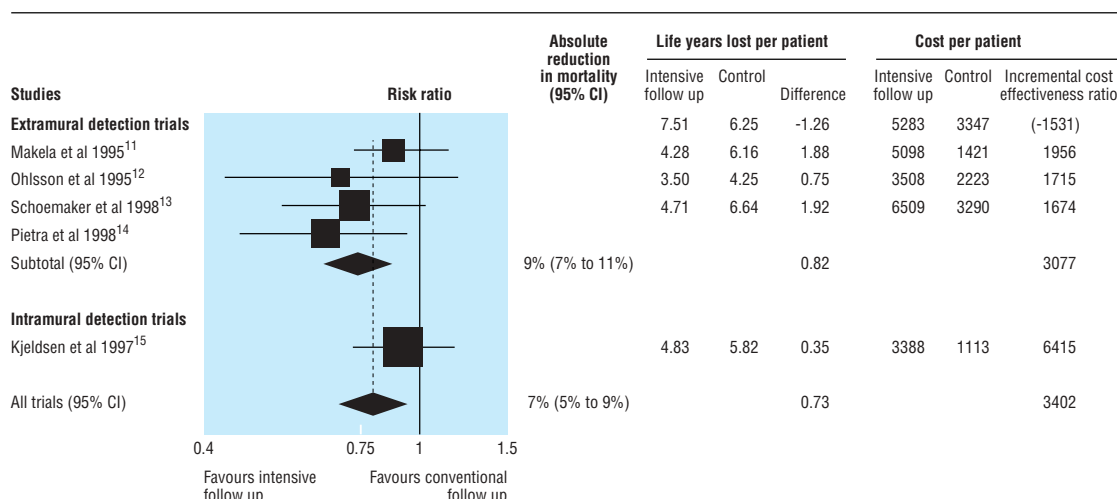
Sensitivity analyses
We undertook several sensitivity analyses to illustrate the impact of the principal aspects of uncertainty on the estimate of cost effectiveness. These included, separately and together, changes to discount rates as proposed by the US Panel on Cost Effectiveness in Health and Medicine,[24] distributions of deaths (constant number, constant rate, and all deaths at end of five years), false positive test rates, and maximum surveillance and treatment costs.

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 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

Cost effectiveness
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 incremental 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.[5] 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

Studies	Risk ratio	Absolute reduction in mortality (95% CI)	Life years lost per patient			Cost per patient		
			Intensive follow up	Control	Difference	Intensive follow up	Control	Incremental cost effectiveness ratio
Extramural detection trials			7.51	6.25	-1.26	5283	3347	(-1531)
Makela et al 1995[11]			4.28	6.16	1.88	5098	1421	1956
Ohlsson et al 1995[12]			3.50	4.25	0.75	3508	2223	1715
Schoemaker et al 1998[13]			4.71	6.64	1.92	6509	3290	1674
Pietra et al 1998[14]								
Subtotal (95% CI)		9% (7% to 11%)			0.82			3077
Intramural detection trials								
Kjeldsen et al 1997[15]			4.83	5.82	0.35	3388	1113	6415
All trials (95% CI)		7% (5% to 9%)			0.73			3402

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[5]). Data are categorised into extramural and intramural detection groups. Positive difference indicates time gained (improved survival). See 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]

corresponding values for the four trial model were £2529 and £3077, suggesting that targeted surveillance is more cost effective.

Changes in benefit and discount rates and in false positive test rates made little impact on the incremental cost effectiveness ratios in both models (data for four trial model not shown; table 2). Changing the distributions of deaths yielded similar incremental cost effectiveness ratios, suggesting that the assumptions within the primary models were robust. Worst case scenario analyses showed that substituting with maximum surveillance costs produced greater increases in incremental cost effectiveness ratios compared with substituting with maximum treatment costs, indicating that surveillance cost is the most important determinant of cost effectiveness. All incremental cost effective-

ness ratios for maximum cost estimates fell within the NHS cost acceptability threshold. 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

Table 2 Sensitivity analyses

Model	Costs per patient (£)		Extra costs	Incremental cost effectiveness ratio
	Intensive follow up	Control		
Five trial model				
Base case*	4 758	2279	2479	3 402
Different discounts:				
Undiscounted	5 173	2417	2756	3 540
Benefits and costs discounted at 3%	4 953	2344	2609	3 832
Distribution of death:				
Constant rate	4 721	2255	2467	3 285
All deaths at end of five years	5 160	2471	2689	4244
False positive test rate:				
Zero rate (no false positives)	4 757	2279	2479	3 402
Rate at 30%	4 758	2279	2479	3 403
Maximum costs:				
Surveillance	12 310	5033	7277	9 989
Treatment	8 874	5836	3038	4 171
Surveillance and treatment	16 426	8589	7837	10 757
Four trial model (targeted)				
Base case*	5 100	2570	2529	3 077
Maximum costs:				
Surveillance	13 403	5917	7486	9 108
Treatment	9 509	6390	3119	3 794
Surveillance and treatment	17 813	9737	8076	9 825

£1 (€1.4; $1.7).
Estimates are costs for each patient followed, assuming all patients started follow up.
*Survival analysis at constant number of deaths for each time period, false positive test rate at 15%, benefit effect discount at 1.5%, and cost discount at 6%.

estimates of the cost of intensive follow up. The data also show that targeted follow up improves cost effectiveness.

Strengths compared with other studies

Previous studies have examined economic issues related to follow up after treatment for colorectal cancer,[28–33] but predated the effectiveness data provided by the two recently published meta-analyses.[5 6] 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. Further strengths were the robustness of the results: adjustments to maximise costs yielded incremental cost effectiveness ratios well within the threshold for NHS cost acceptability, the incremental cost threshold was high (ninefold increases), and the thresholds of effectiveness were 3% for both models.

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

Study limitations

The first limitation of our study was the clinical heterogeneity of follow up regimens among the five trials.[5] No study directly compared specific tests, and therefore it was not possible to evaluate the cost effectiveness of specific surveillance tools. A second limitation was the lack of quality of life data for follow up of patients with colorectal cancer, although one study has assigned a quality adjusted life year of 0.83 based on data from a chemotherapy trial.[29] As intensive follow up does not significantly raise patient anxieties, this may prove a reasonable estimate, but further studies are required before these values can be incorporated into health economic calculations.[34] 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 thus 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 absolute no follow up (zero surveillance costs), although in modern practice the acceptability of a no follow up strategy is questionable.[35]

Implications for health policy

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.[18 36 37] Moreover, compared with population screening, these patients are self defined, well motivated, and compliant.[38]

Factors that could affect future results

Large randomised trials are needed to evaluate the efficacy of specific surveillance tools.[5 35] 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 as a proportion of patients with recurrences undergoing salvage therapy will have delayed second recurrences. Secondly,

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> ### 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

the included trials predated the widespread use of chemotherapy for advanced colorectal cancer or as an adjunct to salvage reoperation, approaches that may improve survival.[39] This potential improvement in effectiveness will be coupled with increased costs. However, as maximising treatments costs (without changes in surveillance costs) had only minor effects on incremental cost effectiveness ratios, it is tempting to speculate that chemotherapy, expensive when considered in selected groups, may be cost effective in the wider context.[39] Thirdly, our analysis treated 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 are important determinants of compliance in screening for colorectal cancer and may thus be relevant in cancer surveillance.[40] 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 from factors other than salvage for recurrent disease—for example, psychosocial or improved treatment of coincidental disease. Evidence from our meta-analysis shows that some reductions in all cause mortality associated with intensive follow up are attributable to factors other than salvage therapy (unpublished data).[5]

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