A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent

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Scientific summary

The FACS RCT

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Scientific summary

Background

The original protocol for the FACS (Follow-up After Colorectal Surgery) trial specified the main outcome as overall mortality based on 1200 patients randomised to each intervention arm and followed up for 5 years. It was planned to recruit 2400 participants in each factorial group (4800 total) to detect a 4% improvement from 49% to 53% in each factorial comparison [carcinoembryonic antigen (CEA) testing vs. no CEA testing, computerised tomography (CT) vs. no CT]. Difficulties in recruitment were encountered from the outset. Despite a major expansion in the number of centres recruiting and a substantial protocol amendment to reflect changing clinical views on the position of equipoise (a single CT scan at the investigator's discretion 12–18 months post randomisation was added to the follow-up schedule for the minimum follow-up arm), many clinicians and patients had concerns regarding participation. In addition, it was noted that the overall mortality was much lower than expected. On this basis, after interim review of 500 participants, the Data Monitoring and Ethics Committee (DMEC) advised that the sample size be reduced to 1180 in total and that the primary outcome be changed to 'surgical treatment of recurrence with curative intent'. Finally, owing to a significant interaction, the primary analysis was altered from factorial to a three-way comparison between each of the three intensively monitored groups and the group with no additional monitoring (apart from a single CT scan).

The Health Technology Assessment programme accepted this proposal for a surrogate end point and recruitment was stopped in July 2009, when just over 1200 participants had entered the trial. In August 2012, when all participants had completed 3 years of scheduled follow-up, the randomisation code was broken at the recommendation of the DMEC and an interim analysis was conducted. This analysis showed that intensive follow-up increased, by approximately threefold, the number of patients with recurrence who could be treated surgically with curative intent, but there was no significant difference in overall survival. The further analysis reported here is based on data collected up to the end of November 2014, when all surviving participants had completed the scheduled 5 years of follow-up and the median time elapsed since the recruitment of each participant was 8.7 years (range 5.5 to 11.9 years). The one exception is the observational analysis of recurrence, which is based on the data available at the time of the interim analysis.

Aim and objectives

Aim

To assess whether or not augmenting symptomatic follow-up in primary care with two intensive methods of follow-up (monitoring of blood CEA levels in primary care and scheduled imaging in hospital) is clinically effective and cost-effective in detecting the recurrence of colorectal cancer treatable surgically with curative intent and in improving survival.

Specific objectives

1. To estimate the effect of 3- to 6-monthly measurement of blood CEA levels and 6- to 12-monthly CT imaging plus an additional colonoscopy on:

    i. the number and cost of detecting recurrences treatable surgically with curative intent
    ii. overall and colorectal cancer-specific mortality
    iii. cost per quality-adjusted life-year (QALY) saved.

2. To describe in trial participants:

   i. the frequency and pattern of recurrence by site and stage of the primary tumour
   ii. the length of post-recurrence survival by treatment intent
   iii. the cost of NHS services utilised
   iv. health-related quality of life (HRQoL) during follow-up.

Methods

Design

A randomised controlled trial with a 2 × 2 factorial design; participants were randomised independently to (1) CT imaging every 6–12 months or at minimum follow-up and (2) blood testing to measure CEA levels every 3–6 months or at minimum follow-up.

Participants

The trial was conducted in 39 NHS hospitals in England that had access to high-volume regional services geared towards offering surgical treatment for metastatic recurrence. The participants were recruited between January 2003 and August 2009. All of the participants had undergone curative treatment for primary colorectal cancer with no residual disease, microscopically clear margins and Dukes' A to C stage (tumour, node, metastasis stage I–III). Patients were excluded if they had concurrent serious illness, dominantly inherited colon cancer or an inability to give written informed consent or if they were involved in a primary treatment trial with conflicting follow-up requirements.

Interventions

Follow-up was scheduled for 5 years from trial entry. Patients received one of four types of follow-up: (1) CEA testing follow-up – 3-monthly measurement of blood CEA for 2 years and then 6-monthly measurement for 3 years, with a single chest, abdominal and pelvic CT scan at 12–18 months; (2) CT follow-up – chest, abdominal and pelvic CT scan 6-monthly for 2 years and then annually for 3 years; (3) CEA testing and CT follow-up – both blood CEA measurement and CT imaging as above; and (4) minimum follow-up – no scheduled follow-up except a single chest, abdominal and pelvic CT scan at 12–18 months if requested at study entry by the hospital clinician (187, 62% received a CT scan). All patients were offered an end-of-trial colonoscopy at 5 years; in the two CT arms, a colonoscopy to check for luminal recurrence or metachronous primary cancer was also undertaken at 2 years.

Primary clinical outcome

Surgical treatment of identified recurrence with curative intent. Data on treatment of recurrence and treatment intent were recorded on case report forms (CRFs) by local National Cancer Research Network staff (who had access to the full clinical records).

Secondary clinical outcomes

(1) Overall survival, (2) deaths from colorectal cancer, (3) time to detection of recurrence and (4) post-recurrence survival. Information on deaths was collected by flagging each participant at the Office for National Statistics (ONS) central registry; cause of death was abstracted from death certificates.

Economic outcomes

The discounted total number of QALYs gained over the 5 years of follow-up was the primary outcome measure for the cost-effectiveness analysis. The secondary outcomes were (1) resource use, (2) NHS costs and (3) HRQoL. QALYs were calculated by applying the average index score of HRQoL to the observed survival in each year.

Sample size

To detect a 6% absolute difference in the primary outcome between minimum follow-up and any of the three other more intensive follow-up arms with 80% power (two-sided alpha 0.05) was estimated to require 205 patients in each of the four follow-up arms; 590 subjects allocated to each factorial group (CEA measurement and CT imaging) were estimated to provide 80% power to detect a 3% absolute difference in the factorial comparison. We therefore planned to stop recruitment when we reached a minimum of 1180 participants.

Randomisation

Patients were independently allocated at random on a 1 : 1 ratio to receive or not receive each of the factorial interventions (CEA measurement and hospital-based imaging) using the telephone randomisation service provided by the Oxford Clinical Trials Unit. A computerised algorithm was applied using the method of minimisation to balance patient characteristics within each centre; the balancing variables were adjuvant chemotherapy, gender and age group (three strata).

Statistical methods for clinical analyses

When feasible, crude data are presented with statistical comparison made between randomisation arms based on chi-squared tests for binary or categorical data, the *t*-test or analysis of variance as appropriate for comparing group means and the Kruskal–Wallis test for comparing medians. Time to recurrence was analysed by the Kaplan–Meier method, to take account of both time-censoring and the difference in the number of recurrences detected in each arm. The plots of time to recurrence are compared by the log-rank Mantel–Cox statistic. Adjusted odds ratios (ORs) for the main outcome were calculated by binary logistic regression; Cox HRs are also reported for comparison of overall mortality. The primary analysis was undertaken using IBM Statistical Product and Service Solutions (SPSS) version 20 (IBM Corporation, Armonk, NY, USA).

Statistical methods for economic analyses

The analysis was conducted from the perspective of the UK NHS, with national average unit costs (expressed in 2012–13 UK pounds sterling) obtained from a variety of sources and applied to patient-level resource-use volumes to derive costs per patient. As the time horizon for the analysis was 5 years, costs and QALYs were discounted to present values at an annual rate of 3.5%. Multiple imputation using chained regression equations were used to impute missing values. An incremental cost-effectiveness ratio (ICER) was computed and compared against the cost-effectiveness threshold specified by the National Institute for Health and Care Excellence (£20,000–30,000 per QALY). Non-parametric bootstrapping was used to generate cost-effectiveness acceptability curves. All economic analyses were performed using Stata® version 12 (StataCorp LP, College Station, TX, USA).

Protocol adherence and withdrawal

Adherence to protocol was ascertained through NHS hospital and laboratory records. A secondary per-protocol analysis is reported that excludes the 308 patients who received any unscheduled investigation or had missed more than one scheduled examination. Reasons for withdrawal were sought. All patients who withdrew gave their consent for continued follow-up through ONS mortality records. The analysis of other clinical outcomes (including recurrence and recurrence treated surgically with curative intent) is censored on the date of withdrawal.

Clinical results

Detection of recurrence

During the 5 years of scheduled follow-up, cancer recurrence was detected in 203 (16.9%) participants. Two-thirds of recurrences (134, 66.0%) were detected by a scheduled follow-up investigation: 88 (64.7%) by CT, 43 (31.6%) by CEA testing and five at colonoscopy (either by colonoscopy or by another investigation

initiated at the consultation) (2.98%). Fewer recurrences were detected in the minimum arm than in the intensive follow-up arms (12.6% vs. 18.3%; $p = 0.02$).

Recurrence treatable with curative intent

The proportion of participants with recurrence surgically treated with curative intent was 6.3% (76/1202) overall, with little difference according to Dukes' staging (stage A, 5.1%; stage B, 7.4%; stage C, 5.6%; $p = 0.56$). The proportion was two to three times higher in each of the three more intensive follow-up arms (7.5% overall) than in the minimum follow-up arm (2.7%) (absolute difference 4.8%; $p = 0.003$). The adjusted OR in the factorial comparison was 2.5 for CEA testing only ($p = 0.04$) and 3.7 for CT only ($p = 0.002$). There was no evidence of any additive effect (the adjusted OR for the combined CT and CEA testing arm was not significantly different from that for CT or CEA testing alone).

Post-recurrence survival

The number of patients with recurrence detected during scheduled follow-up who were still alive at the time of analysis was higher in intensive follow-up arms (4.8% vs. 2.3%; $p = 0.07$), as was the median post-recurrence survival (27.3 vs. 14.6 months; $p = 0.11$), but neither difference is statistically significant. Of the patients with recurrence treated with curative intent, 53% were alive at the end of follow-up.

Overall survival

Total mortality at a median of 8.7 years post randomisation in each group was as follows: CEA testing, 63 deaths (33%); CT, 80 deaths (32%); CEA testing and CT, 63 deaths (27%); and minimum follow-up, 52 deaths (28%). There were no significant differences in the total number of deaths, or in the number of deaths attributed to colorectal cancer, between the four randomisation arms or two factorial groups. The Kaplan–Meier overall survival analysis showed no significant difference in survival over time between arms (log-rank $p = 0.45$). The baseline-adjusted Cox hazard ratio (HR) comparing the minimum and intensive arms showed a non-significant survival advantage for minimum follow-up of 0.87 [95% confidence interval (CI) 0.67 to 1.15]. These CIs suggest an upper limit to the absolute mortality benefit from intensive follow-up of 3.8%; the lower limit means that it is impossible to exclude the possibility of harm, although this is unlikely to be based on the survival of patients treated with curative intent.

Observational analysis of recurrence by site

This analysis was based on 189 patients with recurrence in the 2012 data set. The incidence of recurrence varied according to the site of the primary (right colon, 51/379, 14%; left colon, 68/421, 16%; rectum, 70/332, 21%; $p = 0.023$) and initial stage (Dukes' A, 26/249, 10%; Dukes' B, 81/537, 15%; Dukes' C, 82/346, 24%; $p < 0.0001$). Recurrences from lower-stage cancers were more likely to be treatable with curative intent (Dukes' A, 13/26, 50%; Dukes' B, 32/81, 40%; Dukes' C, 20/82, 24%; $p = 0.03$). Those with rectal cancers benefited most from follow-up (proportion with treatable recurrence: rectum, 30/332, 9%; left colon, 23/421, 6%; right colon, 12/379, 3%; $p = 0.003$). Both initial stage (log-rank $p = 0.005$) and site of primary cancer (log-rank $p = 0.01$) influenced post-recurrence survival.

Economic results

The incremental cost per patient treated surgically with curative intent compared with minimum follow-up was £40,131 with CEA testing, £43,392 with CT and £85,151 with CEA testing and CT. However, the lack of differential impact on survival means there was little difference in QALYs saved between the minimum follow-up [3.61, standard error (SE) 0.07] and intensive arms (CEA testing 3.66, SE 0.06; CT 3.62, SE 0.07; CEA testing and CT 3.59, SE 0.07). Consequently, the overall mean (SE) patient costs per QALY saved were lower in the minimum follow-up arm [£3138 (£334)] than in the more intensive arms [£4613 (£438) CEA testing; £6048 (£393) CT; £6796 (£618) CEA testing and CT]. The additional cost per QALY gained of moving from minimum follow-up to CEA testing was £25,951 and for CT was £246,107. When compared with minimum follow-up, combined CEA testing and CT was more costly and generated fewer QALYs resulting in a negative ICER (–£208,347) and a dominated policy.

Conclusion

The proportion of participants with recurrence treated with curative intent was lower than predicted from previous trials (6.0% overall), but it was three times higher in the more intensive follow-up arms than in the minimum follow-up arm. Both CEA testing (with a single CT scan) and regular CT imaging are effective modes of follow-up, but combining regular CEA testing and CT imaging provided no additional benefit. There was no statistical difference in overall deaths or colorectal cancer deaths in the minimum compared with the intensive follow-up arms after a median of 8.7 years of observation. The CIs around the HR show that if there is a survival benefit from intensive follow-up in the first 10 years it is very unlikely to exceed 4% in absolute terms and harm cannot be excluded. Of the intensive follow-up strategies, CEA testing has the lowest cost per treatable recurrence detected and the lowest cost per QALY gained when compared with minimum follow-up. However, a longer time horizon is required to ascertain whether or not identifying more curatively treatable recurrences offers a survival benefit and thus a more efficient use of scarce health-care resources than minimum follow-up.

Trial registration

This trial is registered as ISRCTN41458548.

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