Original Investigation

Effect of 3 to 5 Years of Scheduled CEA and CT Follow-up to Detect Recurrence of Colorectal Cancer
The FACS Randomized Clinical Trial

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IMPORTANCE Intensive follow-up after surgery for colorectal cancer is common practice but is based on limited evidence.

OBJECTIVE To assess the effect of scheduled blood measurement of carcinoembryonic antigen (CEA) and computed tomography (CT) as follow-up to detect recurrent colorectal cancer treatable with curative intent.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial in 39 National Health Service hospitals in the United Kingdom; 1202 eligible participants were recruited between January 2003 and August 2009 who had undergone curative surgery for primary colorectal cancer, including adjuvant treatment if indicated, with no evidence of residual disease on investigation.

INTERVENTIONS Participants were randomly assigned to 1 of 4 groups: CEA only (n = 300), CT only (n = 299), CEA+CT (n = 302), or minimum follow-up (n = 301). Blood CEA was measured every 3 months for 2 years, then every 6 months for 3 years; CT scans of the chest, abdomen, and pelvis were performed every 6 months for 2 years, then annually for 3 years; and the minimum follow-up group received follow-up if symptoms occurred.

MAIN OUTCOMES AND MEASURES The primary outcome was surgical treatment of recurrence with curative intent; secondary outcomes were mortality (total and colorectal cancer), time to detection of recurrence, and survival after treatment of recurrence with curative intent.

RESULTS After a mean 4.4 (SD, 0.8) years of observation, cancer recurrence was detected in 199 participants (16.6%; 95% CI, 14.5%-18.7%) overall; 71 of 1202 participants (5.9%; 95% CI, 4.6%-7.2%) were treated for recurrence with curative intent, with little difference according to Dukes staging (stage A, 5.1% [13/254]; stage B, 6.1% [34/553]; stage C, 6.2% [22/354]). Surgical treatment of recurrence with curative intent was 2.3% (7/301) in the minimum follow-up group, 6.7% (20/300) in the CEA group, 8% (24/299) in the CT group, and 6.6% (20/302) in the CEA+CT group. Compared with minimum follow-up, the absolute difference in the percentage of patients treated with curative intent in the CEA group was 4.4% (95% CI, 1.0%-7.9%; adjusted odds ratio [OR], 3.00; 95% CI, 1.23-7.33), in the CT group was 5.7% (95% CI, 2.2%-9.5%; adjusted OR, 3.63; 95% CI, 1.51-8.69), and in the CEA+CT group was 4.3% (95% CI, 1.0%-7.9%; adjusted OR, 3.10; 95% CI, 1.10-8.71). The number of deaths was not significantly different in the combined intensive monitoring groups (CEA, CT, and CEA+CT; 18.2% [164/901]) vs the minimum follow-up group (15.9% [48/301]; difference, 2.3%; 95% CI, −2.6% to 7.1%).

CONCLUSIONS AND RELEVANCE Among patients who had undergone curative surgery for primary colorectal cancer, intensive imaging or CEA screening each provided an increased rate of surgical treatment of recurrence with curative intent compared with minimal follow-up; there was no advantage in combining CEA and CT. If there is a survival advantage to any strategy, it is likely to be small.

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Colorectal cancer is a major cause of morbidity and mortality. It is the third most common cancer worldwide, with 1.24 million cases reported to the International Agency for Research on Cancer in 2008.[1] Traditionally, patients who have had curative treatment for colorectal cancer undergo regular hospital follow-up for at least 5 years to detect recurrence. Although locoregional relapse is traditionally associated with poor prognosis, specialist centers are reporting improved cure rates for selected patients with combined-mode treatment.[2] Success in treating metastatic recurrence has also been increasing. Approximately 40% of patients survive 5 years after complete resection of liver metastases[3] and comparable results have been reported for lung metastases.[4] The likelihood of survival is increased if metastatic disease is treated before it becomes symptomatic.[5]

Seven published clinical trials have compared different follow-up regimens.[6-12] Two systematic reviews suggest an overall survival benefit associated with more intensive follow-up.[13,14] However, trial quality was modest, the estimated effect on disease-specific survival was not statistically significant, and the mechanism by which the substantial survival benefits reported were achieved is unclear. Two reviews[13,14] concluded that the existing evidence base needed to be strengthened by high-quality trials addressing the effectiveness of the individual components of follow-up.

The 2 individual components of follow-up recognized to be widely available and affordable and to have the potential to detect isolated metastatic recurrence at an early and surgically treatable stage are computed tomography (CT) imaging of the chest, abdomen, and pelvis and regular blood carcinoembryonic antigen (CEA) measurement. The FACS (Follow-up After Colorectal Surgery) trial was commissioned by the UK National Institute for Health Research Health Technology Assessment program to assess the effect of these 2 modes with the intention of providing a sound evidence base to inform clinical practice. The original intention was to conduct a trial of sufficient size to assess survival advantage but when this proved infeasible, detection of recurrence that was treatable surgically with curative intent was chosen as the main outcome measure. Pretrial modeling suggested that unless follow-up increased the number of such recurrences detected, an important survival advantage of follow-up would not be achieved.

Methods

Trial Design

The FACS trial was a factorial 2×2 pragmatic randomized clinical trial conducted in 39 centers in the United Kingdom; participants were randomized independently to CT imaging every 6 to 12 months or minimum follow-up and to CEA testing every 3 to 6 months or minimum follow-up.

Participants

To enroll in the trial, all participants had to have undergone curative treatment for primary colorectal cancer with no residual disease, microscopically clear margins, and Dukes stage A to C (TNM stage 1-3). Patients were disease-free based on colonic imaging with no evidence of metastatic disease (confirmed by CT or magnetic resonance imaging liver scan and chest CT scan) and with a postoperative blood CEA level of 10 µg/L or less following surgery or completion of adjuvant therapy as indicated.

Patients were excluded if they had concurrent serious illness or dominantly inherited colon cancer, were unable to provide written informed consent, or were involved in a primary treatment trial with conflicting follow-up requirements. Potential participants younger than 50 years or more than 6 months from completion of primary or adjuvant treatment were included only if agreed on by the chief surgical investigator.

All participants gave written informed consent to participate in the trial. Ethical approval for the trial was granted by the National Health Service (NHS) South-West Research Ethics Committee.

Study Setting

Participants were recruited at 39 NHS hospitals in the United Kingdom with access to high-volume regional services geared to offer surgical treatment for recurrence.

Interventions

Follow-up was scheduled to occur for 5 years after trial entry. The factorial design, with independent allocation to the CEA and CT interventions, meant that patients received 1 of 4 types of follow-up:

1. CEA follow-up: measurement of blood CEA every 3 months for 2 years, then every 6 months for 3 years, with a single chest, abdomen, and pelvis CT scan at 12 to 18 months if requested at study entry by hospital clinician
2. CT follow-up: CT of the chest, abdomen, and pelvis every 6 months for 2 years, then annually for 3 years
3. CEA and CT follow-up: both blood CEA measurement and CT imaging as above
4. Minimum follow-up: no scheduled follow-up except a single CT scan of the chest, abdomen, and pelvis at 12 to 18 months if requested at study entry by the hospital clinician

All patients had undergone colonoscopy at trial entry to ensure there was no residual intraluminal disease and were offered an end-of-trial colonoscopy at 5 years; in the 2 CT groups, an additional colonoscopy was undertaken at 2 years.

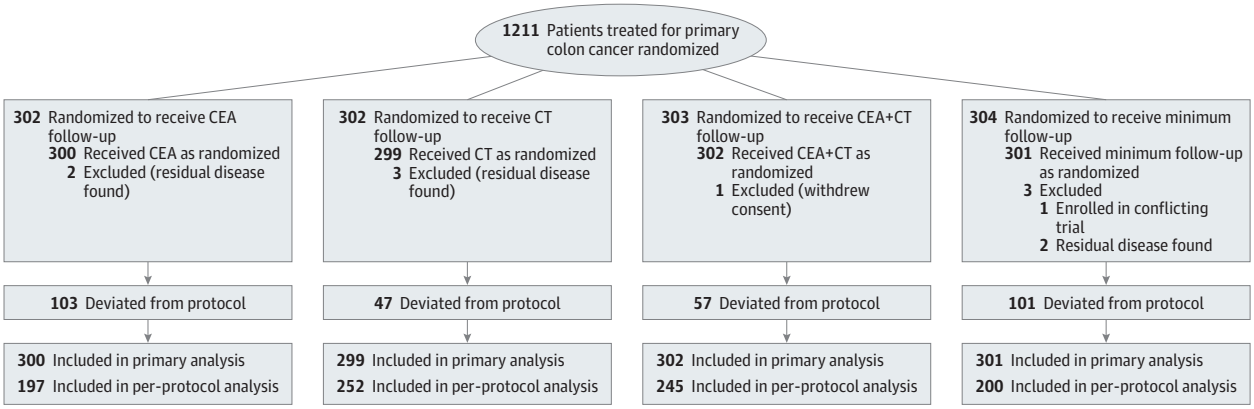
Blood collection kits were sent directly to patients, who then attended their own general practice for phlebotomy. Blood was sent to the biochemistry laboratory at the John Radcliffe Hospital, Oxford; the CEA analysis was performed using a Siemens Centaur XP analyzer. If a patient's blood CEA level was 7 µg/L or more above the level at trial entry, the test was repeated as soon as possible; if the second test result was also greater than this threshold, the patient's general practice physician was asked to refer the patient urgently to the local hospital.

Outcomes

The primary outcome was surgical treatment of recurrence with curative intent after a minimum of 3 years of follow-up. Secondary outcomes were mortality (total deaths and deaths due to colorectal cancer), time to detection of recurrence, and survival after treatment of recurrence with curative intent.

Information on participant deaths was collected at the Office for National Statistics central registry (all patients were reg-

Figure 1. Participant Flow



It was not feasible to collect information on the number of potentially eligible patients excluded from the trial. For the primary intention-to-treat analysis, mortality data were available through the NHS central registry for all participants; the potential completeness of ascertainment of recurrence is reported in Table 2. For the per-protocol analysis, details of the deviations from the follow-up intervention resulting in exclusion are given in eTable 1 in the Supplement.

istered to have the trials unit notified in the event of the patient's death); cause of death was abstracted from death certificates. Data on treatment of recurrence and treatment intent were recorded on case report forms by local National Cancer Research Network staff who had access to the full clinical records.

Randomization and Blinding

Randomization to 1 of 4 groups (**Figure 1**) on a 1:1:1:1 ratio was performed centrally at the Oxford Clinical Trials Unit using a minimization algorithm to balance patient characteristics within each center based on 3 variables: adjuvant chemotherapy, sex, and age group. Study nurses contacted the Oxford Clinical Trials Unit by telephone to enter a patient in the trial, reporting the relevant patient characteristics; they were then told the trial group to which the patient had been allocated.

Because this was a pragmatic open trial, it was not possible to conceal the allocation group from either participants or clinicians. However, the research staff who abstracted outcome data from clinical notes were employed by the local National Cancer Research Network teams independent of the investigators. The analysis program was undertaken first using dummy variables for the allocation groups and the code was not broken until the precise procedures for analysis were agreed on.

Sample Size

From the run-in phase of the trial, it was predicted that 2% of patients in the minimal follow-up group would have undergone surgery for recurrence with curative intent by 3 years of follow-up. It was therefore estimated that a sample size of 590 participants would need to be allocated to each factorial group to achieve 80% power with a 2-sided α=.05 to detect a minimum 3% absolute effect of intensive monitoring with CT or CEA. Modeling suggested that a 3% difference in treatment with curative intent translated into overall survival was the smallest difference that would prove cost effective. To compare the minimum intervention group with each of the CEA, CT, and CEA+CT groups separately, this sample size would provide 51%, 70%, and 84% power to detect absolute differences of 3%, 4%, and 5%, respectively. We therefore decided to stop recruitment when the sample size reached a minimum of 1180 participants.

Statistical Analysis

The primary analysis was an intention-to-treat comparison of the proportion of patients experiencing recurrence who were treated surgically with curative intent (1) comparing all patients randomized to the 3 intensive follow-up groups (CEA only, CT only, and CEA+CT) with the minimum follow-up group and (2) comparing all patients randomized to the 2 factorial groups (CEA vs no CEA and CT vs no CT). When feasible, crude data are presented with statistical comparison made between randomization groups based on χ^2 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 analyzed by the Kaplan-Meier method to take account of both time censoring and the difference in the number of recurrences detected in each group (ie, a crude comparison of time to recurrence may be misleading because this approach does not take into account recurrences not yet detected in less-effective follow-up groups). The plots of time to recurrence were compared by the log-rank Mantel-Cox statistic. Adjusted odds ratios for the main outcome were calculated by binary logistic regression, entering all the baseline characteristics reported in **Table 1** into the model. For the comparison of factorial groups (CEA vs minimum follow-up and CT vs minimum follow-up), an interaction term (CEA factor × CT factor) was also entered. We set a statistical significance threshold of α=.05 based on 2-sided tests. The analyses were conducted using IBM SPSS version 20.

Protocol Adherence and Amendments

Adherence to protocol was ascertained through NHS hospital and laboratory records. A secondary per-protocol analysis was conducted excluding patients who received any unscheduled investigation or had missed more than 1 scheduled examination. There were 2 significant amendments to the original protocol during

Table 1. Characteristics of Participants at Trial Entry by Randomization Group and Factorial Group

Characteristics	Individual Randomization Group				Factorial Comparison Group			
	CEA Only (n=300)	CT Only (n=299)	CEA+CT (n=302)	Minimum Follow-up (n=301)	CEA (n=602)	No CEA (n=600)	CT (n=601)	No CT (n=601)
Age, y								
Mean (SD)	68.8 (8.3)	69.0 (8.9)	69.5 (8.1)	69.3 (8.5)	69.2 (8.2)	69.1 (8.7)	69.2 (8.5)	69.1 (8.4)
Median (IQR)	69 (63-75)	69 (62-76)	70 (64-76)	70 (63-75)	69 (63-75)	70 (63-76)	70 (63-76)	69 (63-75)
Male, No. (%)	184 (61.3)	183 (61.2)	185 (61.3)	184 (61.1)	369 (61.3)	367 (61.2)	368 (61.2)	368 (61.2)
Concurrent treatment for other illness, No. (%)	90 (30.0)	81 (27.1)	86 (28.5)	93 (30.9)	176 (29.2)	174 (29.0)	167 (27.8)	183 (30.4)
Pretreated with chemotherapy, No. (%)	121 (40.3)	118 (39.5)	125 (41.4)	123 (40.9)	246 (40.9)	241 (40.2)	243(40.4)	244 (40.6)
Pretreated with radiotherapy, No. (%)	32 (10.7)	34 (11.5)	38 (12.8)	35 (11.7)	70 (11.7)	69 (11.6)	72 (12.1)	67 (11.2)
Site of cancer, No. (%)[a]	(n=293)	(n=290)	(n=292)	(n=295)	(n=585)	(n=585)	(n=582)	(n=588)
Right colon	93 (31.7)	96 (33.1)	90 (30.8)	103 (34.9)	183 (31.3)	199 (34.0)	186 (32.0)	196 (33.3)
Left colon	118 (40.3)	96 (33.1)	110 (37.7)	105 (35.6)	228 (39.0)	201 (34.4)	206 (35.4)	223 (37.9)
Rectum	82 (28.0)	98 (33.8)	92 (31.5)	87 (29.5)	174 (29.7)	185 (31.6)	190 (32.6)	169 (28.7)
Dukes stage, No. (%)[b]	(n=289)	(n=293)	(n=287)	(n=292)	(n=576)	(n=585)	(n=580)	(n=581)
A	54 (18.7)	71 (24.2)	60 (20.9)	69 (23.6)	114 (19.8)	140 (23.9)	131 (22.6)	123 (21.2)
B	144 (49.8)	132 (45.1)	146 (50.9)	131 (44.9)	290 (50.3)	263 (45.0)	278 (47.9)	275 (47.3)
C	91 (31.5)	90 (30.7)	81 (28.2)	92 (31.5)	172 (29.9)	182 (31.1)	171 (29.5)	183 (31.5)
Smoking status, No. (%)[c]	(n=290)	(n=288)	(n=294)	(n=290)	(n=584)	(n=578)	(n=582)	(n=580)
Current smoker	20 (6.9)	16 (5.6)	18 (6.1)	14 (4.8)	38 (6.5)	30 (5.2)	34 (5.8)	34 (5.9)
Ex-smoker	145 (50.0)	154 (53.5)	162 (55.1)	155 (53.4)	307 (52.6)	309 (53.5)	316 (54.3)	300 (51.7)
Never smoker	125 (43.1)	118 (41.0)	114 (38.8)	121 (41.7)	239 (40.9)	239 (41.3)	232 (39.9)	246 (42.4)

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; IQR, interquartile range.

[a] Site not specified precisely for 32 participants (2.7%).

[b] Dukes stage not recorded for 41 participants (3.4%). Dukes stage is a measure of the extent of the tumor. Dukes stage A indicates the cancer is only in the innermost lining of the colon or rectum or slightly growing into the muscle layer; Dukes stage B indicates the cancer has grown through the muscle layer of the colon or rectum; and Dukes stage C indicates the cancer has spread to at least 1 lymph node in the area close to the bowel.

[c] Smoking status not recorded for 40 participants (3.3%).

the trial. The initial protocol did not specify the single CT at 12 to 18 months in the minimum follow-up and CEA groups; 66 patients had been randomized to the minimum follow-up group before this change took effect in May 2005. Surgical treatment with curative intent rather than overall survival was specified as the main outcome in 2007 when it became clear that we could not recruit the number of participants necessary to estimate an effect on overall survival with adequate statistical power.

Results

Characteristics of Participants

Allocation of the 1202 eligible participants recruited between January 2003 and August 2009 to each randomization group is shown in Figure 1. The follow-up intervention lasted 5 years or, for patients recruited after August 2007, until August 31, 2012. Characteristics at trial entry are shown in Table 1. The mean age of participants was 69 years, 736 (61.2%) were male, 350 (29.1%) had significant comorbidity; 487 (40.5%) had received adjuvant chemotherapy and 139 (11.6%) preoperative radiotherapy (for rectal cancer) before randomization. The randomization method was successful in achieving a good balance between randomization groups and factorial comparison groups. Cumulative overall survival by stage and randomization group are shown in eFigures 1 and 2, respectively, in the Supplement.

Detection of Recurrence

During the period of observation for recurrence (mean, 4.4 [SD, 0.8] years), cancer recurrence was detected in 199 participants (16.6%; 95% CI, 14.5%-18.7%); 41 (3.4%) had locoregional recurrence only and 101 (8.4%) had metastatic disease limited to the lung and/or liver (**Table 2**). The Kaplan-Meier plots in **Figure 2** show that the 3 intensive interventions tended to detect recurrence earlier, although these differences in earlier detection were not statistically significant. There were no recurrences treatable with curative intent detected in the minimum follow-up group after year 2. Two-thirds of recurrences (n=130 [65.3%; 95% CI, 58.7%-71.9%]) were detected by a scheduled follow-up investigation; the remainder were interval cases, presenting symptomatically or incidentally during investigation of concurrent illness. Three luminal recurrences were detected by the 2-year colonoscopy in the groups monitored by CT imaging. Additionally, 3 cancers were detected by the 5-year colonoscopy but these were new cancers and not recurrent disease. The way in which the recurrences were treated is detailed in eTable 1 in the Supplement.

Curative Treatment and Survival

The proportion of participants with recurrence surgically treated with curative intent was 5.9% (71/1202; 95% CI, 4.6%-7.2%) overall, with little difference between participants according to Dukes staging (stage A, 5.1% [13/254]; stage B, 6.1%

Table 2. Duration of Follow-up and Diagnosis of Recurrence by Randomization Group and Factorial Group

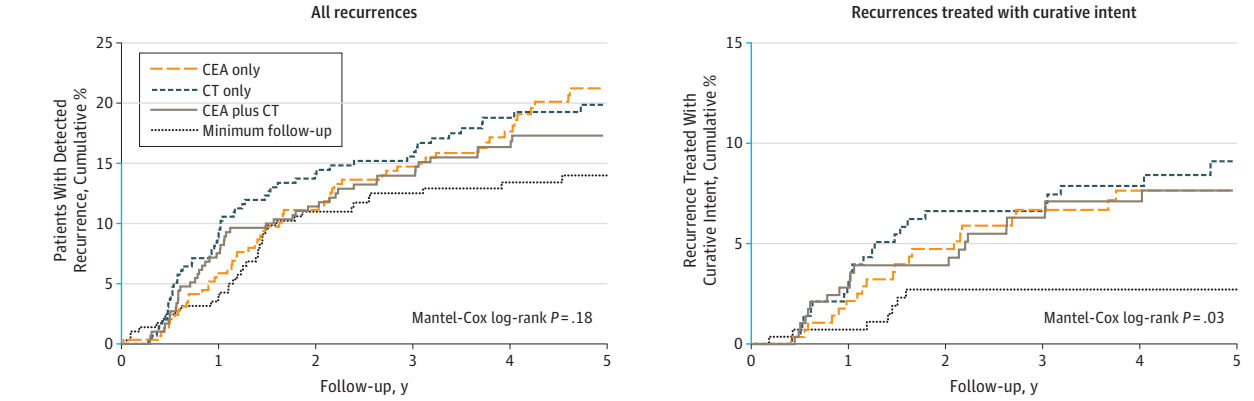
	Individual Randomization Groups					Factorial Comparison Groups					
	CEA Only (n=300)	CT Only (n=299)	CEA+CT (n=302)	Minimum Follow-up (n=301)	*P* Value[a]	CEA (n=602)	No CEA (n=600)	*P* Value[a]	CT (n=601)	No CT (n=601)	*P* Value[a]
Duration of follow-up, mean (SD), y	3.78 (1.53)	3.69 (1.59)	3.74 (1.58)	3.64 (1.69)	.75	3.76 (1.55)	3.67 (1.64)	.33	3.71 (1.59)	3.71 (1.61)	.96
Less than full period of observation, No. (%)[b]	41 (13.7)	39 (13.0)	46 (15.2)	61 (20.3)	.61	87 (14.5)	100 (16.7)	.29	85 (14.1)	102 (17.0)	.18
Diagnosis of recurrence, all sites, No. (%)	57 (19.0)	57 (19.1)	48 (15.9)	37 (12.3)	.08	105 (17.4)	94 (15.7)	.41	105 (17.5)	94 (15.6)	.39
Liver and/or lung only	30	33	25	13		55	46		58	43	
Locoregional only	12	12	11	6		23	18		23	18	
Other metastatic	15	12	12	18		27	30		24	33	
Recurrences detected by scheduled follow-up examination, No. (%)	33 (11.0)	48 (16.1)	40 (13.2)	9 (3.0)	<.001	73 (12.1)	57 (9.5)	.14	88 (14.6)	42 (7.0)	<.001
Blood CEA level	30	0	13	0		43	0		13	30	
CT imaging	3	46	26	9		29	55		72	12	
Colonoscopy	0	2	1	0		1	2		3	0	

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography.

[a] Reported *P* values are based on the Pearson χ^2 test for binary comparisons, 1-way analysis of variance or independent *t* tests in comparing means.

[b] Participants who died during follow-up without evidence of recurrence (n = 46), withdrew consent or moved from National Health Service to private care (n = 24), developed another primary cancer (n = 36), or for whom case report forms seeking information on recurrence had not been completed for the entire period at risk (n = 78).

Figure 2. Time to Diagnosis of Recurrence by Randomization Group



No. at risk						
CEA only	300	270	249	232	172	122
CT only	299	263	236	226	173	115
CEA plus CT	302	265	246	230	177	123
Minimum follow-up	301	261	235	224	172	119

Y-axis scale shown in blue indicates range from 0% to 15%.

[34/553]; stage C, 6.2% [22/354]). **Table 3** shows that surgical treatment of recurrence with curative intent was higher in each of the 3 more intensive follow-up groups compared with the minimum follow-up group (absolute difference ranged from 4.3% to 5.7%; overall *P* = .02). The adjusted odds ratios were 3.0 (95% CI, 1.2-7.3) for CEA only and 3.6 (95% CI, 1.5-8.7) for CT only. The odds ratio for the combined CEA+CT group was similar to that for CT or CEA alone, providing no evidence that any additive effect is achieved by using both together. The factorial comparison showed an absolute difference between the intervention and comparison groups of 1.4% (95% CI, −1.2% to 4.1%) for CEA and 2.8% (95% CI, 0.2%-5.5%) for CT.

Of the 71 participants treated surgically with curative intent, 30 also received chemotherapy (7 with radiotherapy). Of these patients, 47 (69%; 95% CI, 56.9%-79.5%) were still alive at the time of follow-up (median, 4.4 years after diagnosis of recurrence). The absolute difference in the proportion of patients treated and surviving compared with the minimum follow-up group was 3.3% (95% CI, 0.5%-6.2%) for CEA, 2.0% (95% CI, −0.6% to 4.6%) for CT, and 3.6% (95% CI, 0.7%-6.5%) for CEA+CT (overall *P* = .09). The differences in the factorial comparison were 2.4% (95% CI, 0.3%-4.7%) for CEA and 1.2% (95% CI, 1.0%-3.4%) for CT.

The number of deaths was higher but not significantly different in the more intensive follow-up groups compared with

Table 3. Treatment of Recurrence With Curative Intent and Total Mortality by Randomization Group and Factorial Group (Intention-to-Treat Analysis)

	Individual Randomization Groups					Factorial Comparison Groups					
	CEA Only (n=300)	CT Only (n=299)	CEA+CT (n=302)	Minimum Follow-up (n=301)	*P* Value	CEA (n=602)	No CEA (n=600)	*P* Value	CT (n=601)	No CT (n=601)	*P* Value
Surgical treatment with curative intent, No. (%)	20 (6.7)	24 (8.0)	20 (6.6)	7 (2.3)	.02	40 (6.6)	31 (5.2)	.28	44 (7.3)	27 (4.5)	.04
Adjusted odds ratio (95% CI)[a]	3.00 (1.23-7.33)	3.63 (1.51-8.69)	3.10 (1.27-7.57)	1 [Reference]		1.45 (0.45-4.65)			1.38 (0.43-4.36)		
Wald *P* value	.02	.004	.01			.53			.59		
Surgical treatment with curative intent and still alive, No. (%)	15 (5.0)	11 (3.7)	16 (5.3)	5 (1.7)	.09	31 (5.1)	16 (2.7)	.03	27 (4.5)	20 (3.3)	.30
Adjusted odds ratio (95% CI)[a]	2.88 (1.02-8.14)	2.10 (0.72-6.15)	3.10 (1.10-8.71)	1 [Reference]		2.14 (0.58-7.84)			2.38 (0.64-8.84)		
Wald *P* value	.046	.18	.03			.25			.20		
Total deaths, No. (%)	56 (18.7)	60 (20.1)	48 (15.9)	48 (15.9)	.45	104 (17.3)	108 (18.0)	.74	108 (18.0)	104 (17.3)	.76
Deaths attributed to colorectal cancer, No. (%)	32 (10.7)	35 (11.7)	27 (8.9)	28 (9.3)	.66	59 (9.8)	63 (10.5)	.69	62 (10.3)	60 (10.0)	.85

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography.

[a] The adjusted odds ratios and associated 95% CIs were estimated using logistic regression including all the baseline variables listed in Table 1 in the model. For the factorial group comparison, the odds ratio is also adjusted for interaction with the other randomization factor (eg, the CEA×CT interaction). The standard *P* values based on the χ^2 test for heterogeneity (which tests whether the overall distribution in proportions could have occurred by chance). The Wald *P* values test whether the odds of detecting recurrence in each of the intensive follow-up groups are significantly different from that in the minimum follow-up group.

Table 4. Treatment of Recurrence With Curative Intent and Total Mortality by Randomization Group and Factorial Group (Per-Protocol Analysis)

	Individual Randomization Groups					Factorial Comparison Groups					
	CEA Only (n=197)	CT Only (n=252)	CEA+CT (n=245)	Minimum Follow-up (n=200)	*P* Value	CEA (n=442)	No CEA (n=452)	*P* Value	CT (n=497)	No CT (n=397)	*P* Value
Surgical treatment with curative intent, No. (%)	15 (7.6)	24 (9.5)	18 (7.3)	3 (1.5)	.007	33 (7.5)	27 (6.0)	.37	42 (8.5)	18 (4.5)	.02
Adjusted odds ratio (95% CI)[a]	5.10 (1.43-18.2)	6.71 (1.96-22.9)	5.24 (1.50-18.3)	1 [Reference]		1.41 (0.40-5.04)	1 [Reference]		1.45 (0.41-5.06)	1 [Reference]	
Wald *P* value	.03	.005	.02			.60			.56		
Surgical treatment with curative intent and still alive, No. (%)	10 (5.1)	11 (4.4)	14 (5.7)	3 (1.5)	.15	24 (5.4)	14 (3.1)	.08	25 (5.0)	13 (3.3)	.20
Adjusted odds ratio (95% CI)[a]	3.25 (0.83-12.7)	2.78 (0.74-10.5)	3.87 (1.05-14.3)	1 [Reference]		2.27 (0.53-9.62)	1 [Reference]		2.55 (0.61-10.7)	1 [Reference]	
Wald *P* value	.09	.13	.04			.27			.20		
Total deaths, No. (%)	46 (23.4)	58 (23.0)	43 (17.6)	39 (19.5)	.35	89 (20.1)	97 (21.5)	.63	101 (20.3)	85 (21.4)	.69
Deaths attributed to colorectal cancer, No. (%)	28 (14.2)	33 (13.1)	26 (10.6)	24 (12.0)	.69	54 (12.2)	57 (12.6)	.86	59 (11.9)	52 (13.1)	.58

Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography.

[a] The adjusted odds ratios and associated 95% CIs were estimated using logistic regression, including all the baseline variables listed in Table 1 in the model. For the factorial group comparison, the odds ratio is also adjusted for interaction with the other randomization factor (eg, the CEA×CT interaction). The standard *P* values given for comparison of proportions are based on the χ^2 test for heterogeneity (which tests whether the overall distribution in proportions could have occurred by chance). The Wald *P* values test whether the odds of detecting recurrence in each of the intensive follow-up groups are significantly different from that in the minimum follow-up group.

the minimum follow-up group (18.2% [164/901] vs 15.9% [48/301]; difference, 2.3%; 95% CI, −2.6% to 7.1%), as was the number of disease-specific colorectal cancer deaths (10.4% [94/901] vs 9.3% [28/301]; difference, 1.1%; 95% CI, −2.7% to 5.0%). The Kaplan-Meier survival curves by randomization group and Dukes stage are shown in eFigures 1 and 2 in the Supplement.

Adherence to Protocol

The extent of adherence to the follow-up protocol is shown in eTable 2 in the Supplement. Patient adherence was very good, with only 5.8% (35/602) in the CEA group missing more than 1 scheduled CEA test and 5.0% (30/601) in the CT group missing more than 1 CT scan. Although clinician adherence appears to be lower (10.6% of participants [127/1202] received unscheduled CEA blood tests, 10.6% [127/1202] unscheduled CT scans, and 9.7% [117/1202] unscheduled colonoscopies), the protocol required investigation of any patients presenting with symptoms between scheduled follow-up tests. Substantially more unscheduled tests were performed in patients not receiving regular CT scans, with 16.5% (99/601) vs4.7% (28/601) receiving 1 or more unscheduled CEA tests, 17.6% (106/601) vs 3.5% (21/601) receiving 1 or more unscheduled CT tests, and 15.6% (94/601) vs3.8% (23/601) receiving 1 or more unscheduled colonoscopies.

Per-Protocol Analysis

The results of a per-protocol analysis are shown in **Table 4**, excluding the 308 patients (25.6%) who missed more than 1 scheduled visit or underwent any unscheduled investigation. The results are

consistent with the intention-to-treat analysis but effect estimates are higher: the absolute differences in rate of detection of treatable recurrence in the more intensive follow-up groups compared with the minimum follow-up group were 5.8% to 8.0%.

Discussion

The 2 follow-up tests assessed in this trial were CEA and CT imaging. Meta-analyses have suggested that these are the only modes with significant potential to detect curatively treatable metastatic recurrence in patients with colorectal cancer.[13,14] Clinical and ultrasound examination lack sensitivity whereas magnetic resonance imaging can realistically be applied only to the liver and lacks strong evidence of effectiveness in detecting recurrence.[13,14] Computed tomography–positron emission tomography was not an available technology when this trial was initiated and, because of cost and logistics, would be preferred to standard CT for routine follow-up only if evidence suggested much superior performance. Endoscopic imaging (colonoscopy) was provided to patients in all study groups because it is a standard evidence-based element of follow-up care that can detect metachronous polyps or cancer (and, rarely, intraluminal recurrence).[15]

Our results show that intensive follow-up by either scheduled CEA or CT increased the likelihood of detecting a recurrence that can be treated with curative intent. The absolute difference in the proportion of participants treated with curative intent was approximately 5% in the intention-to-treat analysis and 8% in the per-protocol analysis, suggesting that between 12 and 20 patients need to be followed up to identify 1 potentially curable recurrence. More than two-thirds of the patients treated surgically with curative intent were still alive at a median follow-up of just over 4 years postrecurrence, suggesting that 5-year survival may be more than the 40% previously reported.[3,4]

Although the proportion of recurrences treated with curative intent (and the success of such treatment) is higher compared with earlier reports, the absolute number of treatable recurrences detected is lower.[14] This is not explicable by differences in stage-specific case-mix (detection of recurrences treatable with curative intent was similar irrespective of stage), nor is there any evidence that participants in the FACS trial were at low risk of recurrence within stage (84.5% of stage C participants had received adjuvant chemotherapy). Stage-specific overall survival of participants in this study (eFigure 2 in the Supplement) is comparable with that reported in trials of adjuvant chemotherapy, such as MOSAIC.[16] A more likely explanation for the lower detection of treatable recurrence is the rigor of the investigative procedures undertaken to ensure that no residual cancer was present at trial entry. It suggests that the high rate of early recurrence reported from routine cancer statistics in England and Scandinavia[17] reflects residual disease that would have been detected with more thorough imaging. It probably also explains the greater benefit of intensive follow-up reported in previous trials—follow-up detected residual disease, not recurrence. A key finding of this study is therefore the need to fully stage colorectal cancer before embarking on follow-up.

The comparison between intervention groups suggests that monitoring with CEA combined with a single CT scan at 12 to 18 months is not significantly different from undertaking regular CT scanning. Because CEA testing can be done in primary care, it is likely to be more cost-effective than regular CT imaging. However, imaging is still necessary to confirm recurrence, and in the combined CEA+CT group, two-thirds of recurrences were first detected by CT. The diagnostic performance of CEA as a monitoring test depends on the frequency of testing and the algorithm used to interpret the result. The algorithm applied in the FACS trial (refer for imaging if blood CEA level is 7 μg/L above baseline) achieves good specificity but at the cost of modest sensitivity.[18] An ongoing study is investigating whether a higher sensitivity can be achieved at an acceptable level of specificity by applying a diagnostic algorithm that takes account of change over time and has been applied successfully in interpreting cancer antigen 125 levels when screening for ovarian cancer.[19]

We had planned to report our results after all participants had completed 5 years of follow-up because early analysis increases the risk of lead-time bias. However, there have been no cases of recurrence treatable with curative intent after 2 years of follow-up in the minimum follow-up group, making lead-time bias unlikely in our main comparison. Nevertheless, subject to continuing informed consent from those in the minimum follow-up group, we plan to continue follow-up as planned to increase the precision of our results, particularly in relation to disease-specific mortality and posttreatment survival.

The decision on whether the absolute benefit of follow-up is sufficient to justify its opportunity cost will differ between health economies. The benefits of follow-up appear to be independent of diagnostic stage (because although there are fewer recurrences with better-stage tumors, they are more likely to be curable), suggesting that stage-specific follow-up strategies may not be necessary. However, thorough staging investigation at the end of primary treatment to detect residual disease is still important because a large number of "recurrences" reported in routine series are probably residual disease that should be detected and treated before embarking on follow-up. Because of the detailed investigation performed before trial entry to exclude residual disease, our results also provide data on the timing of recurrence that can strengthen the evidence base for choosing the optimal frequency of testing. Duplication of monitoring tests does not appear to add value; participants in the CEA groups had a single CT at 12 to 18 months, when 3 recurrences were detected, but otherwise there was no suggestion of benefit from monitoring with both CEA and CT.

The size of the trial provides limited precision in estimating survival. With an observed 15.9% mortality rate in the minimum follow-up group, we had only 31% power (with 2-sided α=.05) to detect a 5% effect on survival. Although the observed 2% aggregate survival advantage of the minimum follow-up group vs the more intensive follow-up groups is unlikely to be due to bias (central death registration in the United Kingdom means there was no loss to follow-up), it could be due to chance. An observed absolute 6% increase in surgery with curative intent predicts a 2% to 3% survival advantage with intensive follow-up. The confidence intervals around both the total mortality and colorectal cancer–specific mortality rates indicate that our results are still consistent with this outcome.

Conclusions

Among patients who had undergone curative surgery for primary colorectal cancer, intensive imaging and CEA screening each provided an improved rate of recurrence treated with curative intent compared with minimal follow-up; there was no advantage to combining both strategies. If there is a survival advantage to any strategy, it is likely to be small.

ARTICLE INFORMATION

Author Contributions: Dr Perera and Ms Fuller had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Primrose, Gray, Rose, Corkhill, George, Mant.
Acquisition of data: Primrose, Fuller, Mant.
Analysis and interpretation of data: Primrose, Perera, Gray, Rose, Fuller, George, Mant.
Drafting of the manuscript: Primrose, Gray, George, Mant.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Primrose, Perera, Fuller, Mant.
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Administrative, technical, and material support: Fuller, Corkhill.
Study supervision: Primrose, George, Mant.

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