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Title

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

Tom Treasure[1]
Kathryn Monson[2]
Francesca Fiorentino[3]
Christopher Russell

[1]Clinical Operational Research Unit, University College London

[2] Sussex Health Outcomes, Research & Education in Cancer (SHORE-C)
University of Sussex

[3] Department of Cardiothoracic Surgery, NHLI, Imperial College London

Abstract

Objectives: in patients who have undergone a potentially curative resection of colorectal cancer does a 'second-look' operation to resect recurrence, prompted by monthly monitoring of carcinoembryonic antigen, confer a survival benefit?

Design: randomised controlled trial

Setting: 58 hospitals in the United Kingdom and Europe.

Participants: from 1982 to 1993, 1447 patients were enrolled. After protocol exclusions 1235 were eligible and of them 216 met the criteria for CEA elevation and were randomised to 'Aggressive' or 'Conventional' arms.

Interventions: 'second-look' surgery with intention to remove any recurrence discovered.

Primary outcome measure: survival.

Results: by February 1993, 88/108 patients had died in the 'Conventional' arm compared with 91/108 in the 'Aggressive arm'. The hazard ratio for Conventional to 'Aggressive' arms was 0.84 (95% confidence intervals 0.62-1.13; P=0.25). By 2011 a further 25 randomised patients had died. Kaplan Meier showed no difference in long-term survival.

Conclusions: the trial was closed in 1993 following a recommendation from the Data Monitoring Committee that it was highly unlikely that any survival advantage would be demonstrated for CEA prompted second-look surgery. This conclusion was confirmed by repeat analysis after twenty years.

Strengths and limitations of this study

- The CEA Second-Look Trial was a well planned and carefully executed study with a clear question and a well defined outcome of interest.
- Second-look surgery prompted by the best available indicator of recurrence at the time conferred no survival advantage.
- A further strength, and a reason to publish this trial now, is that it shows that randomised trials in surgery can be done and that the result may be counter the beliefs and expectations of practitioners based on their uncontrolled observations.
- A limitation is that present day means of detection, based on imaging and anatomical localisation, may detect patients with recurrence curable by surgery. It follows that the effectiveness of second-look surgery prompted by new imaging methods cannot be assumed but should be the subject of controlled trials.

Introduction

It was observed during the 1970s that the outlook for patients with colorectal cancer was not as good as many had believed – only one in four patients survived for five years after diagnosis, while radical surgery, when feasible, was curative in under half of the patients [1] and results had not improved in several decades.[2-4] Attempts to improve prognosis by refinements in primary operative techniques had not made a difference[5] and it was considered unlikely that technical modifications would lead to improvement in survival following surgery.[1;2] The objective of the CEA Second-Look Surgery Trial was to determine whether, following potentially curative primary surgery for colorectal cancer, the mortality could be decreased by a policy of second-look surgery prompted by rising serum carcinoembryonic antigen (CEA). The trial ran from 1982 to 1993. That there was no survival advantage was reported in 1994 to the British Oncological Association[6] and was published in a letter to the Journal of the American Medical Association.[7]

Surgery for colorectal cancer recurrence has since become routine both in the form of hepatic resection[8] and pulmonary metastasectomy[9] but without evidence from controlled trials for either practice.[10] When doubts were raised about the security of the evidence in the British Medical Journal in 2007[11] a general belief existed that randomised controlled trials of the effectiveness of resection of liver or lung metastases were not possible and were not needed. These paired beliefs are brought into question by the CEA Second-Look Trial: the presumed benefit of surgery of recurrence was not seen when subjected to a randomised controlled trial.[6;7]

Abandonment of the trial in 1994 and gaining access to the data in 2011

The RIAT restorative authors had been involved in various studies related to surgery for disseminated colorectal cancer[11-13] including a conundrum as to whether discovery of an elevated CEA assay should prompt or be considered a contra-indication to pulmonary metastasectomy.[14] We knew the CEA trial to have been enrolling patients in the 1980s but when we searched the literature for the result of the trial we learned that it had been abandoned in 1994. In 2009 we contacted the chief investigator of the trial and the present director of the unit. The data were initially thought to be irretrievably lost or irrecoverable. However, staff at the trials centre retrieved archived CEA electronic files and the death data were updated. We gained access to anonymised electronic data in 2011. The process of data restoration is described later.

Amongst the documents were listed the members of the trial development group in the 1982 protocol[4] and the contributors to the 1994 manuscript.[15] None of these individuals expressed an interest in resuming work on the trial or were in a position to do so. When we contacted them later to share the restored data with them no one raised any objection but on the contrary encouraged us to publish our findings.

Figure 1 Working Party from the 1982 Protocol

Improving detection and treatment of recurrent disease: the context in1982

A founding principle of the CEA Second-Look Trial was that early detection of recurrent tumour would only be justifiable if further treatment offered the prospect of benefit to the individual patient.[4] It appeared that might be the case in colorectal cancer. There were several reports of 30% five-year survival in selected patients after radical resection of recurrent cancer[3;16;17] and resection was believed to sometimes lead to "cure".[3;16-18]

Routine surgical follow-up had not led to further surgery being shown to be beneficial. First-hand experience of members the CEA Second-Look Trial development group was that of 180 patients, followed up from six months to 15 years, at a total of 2319 out-patient clinic visits, only one patient could be considered to have had a potentially curative second-look operation. [19] Clinical evidence of recurrence usually meant that the tumour would be unresectable at second-look laparotomy[20] and that to re-resect with prospect of benefit, recurrence had to be detected before it was clinically evident[4] but more pro-active clinical follow-up of asymptomatic patients by three monthly sigmoidoscopy, barium enema and chest X-ray (the methods available at the time) had still failed to show improvement in 5-year survival.[21]

The Wangensteen Approach:

During the 1950s the systematic use of a policy-based second operation was reported. Patients at high risk of recurrence (those with Dukes' Stage C tumours) were re-operated on at 6-monthly intervals, resecting recurrence when found, until they were 'tumour free'. If cancer had been found the patients were scheduled for 3rd and more "looks", up to six further abdominal operations, "before the abdomen was free of cancer". Once a patient had undergone a negative laparotomy, no more surgery was recommended. Sixty-four patients with colon or rectal cancer were managed in this way. In 35 (55%) of them the "second-look" laparotomy was negative for the discovery of recurrent cancer, seven of whom subsequently had clinical recurrence. There were four (6%) operative deaths.[22] The CEA trialists concluded that this 'blanket second-look' policy might have produced some "cures" but entailed high rates of negative laparotomy and an unacceptable operative mortality rate.[4]

Figure 2 from Wangensteen 1954

The CEA-prompted Second-Look Approach

CEA had been shown to detect recurrence of colorectal cancer following surgery.[23-28] CEA rose, on average, three months prior to clinical evidence of recurrence[24;27] and there were reports of the use of serial serum carcinoembryonic antigen (CEA) assay to detect asymptomatic recurrences in the belief that curative resection would be possible more frequently.[23-25] Several groups used CEA in this way, and found low false positive rates[20;29] and the resectability rate of the recurrence was higher than when clinical criteria were used to prompt re-operation.[20] In the largest published experience of CEA in a post-operative monitoring role[20;23] resectable recurrent tumour was found in 70% in whom re-operation was prompted by a rise in the serum CEA compared with a quarter of patients undergoing second-look laparotomy prompted by clinical indications. Others had not found CEA to be useful in this post-operative monitoring role. Even if efficacy of CEA detected recurrence was accepted, there was also the unresolved question of effectiveness: if more patients were detected and there were more instances of resectable recurrence, did that lead to better survival and patient benefit? The conflicting interpretations of observational data resulted calls for trials[23;29;30] including within a 1981 NIH Consensus Statement.[28]

Methods: trial intent and design

The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years and to follow them for five years. The study was specifically designed with late randomisation in order to maximise statistical power. It was originally intended to recruit 2,000 patients with the anticipation that about 25% would show a CEA rise as the first evidence of possible recurrence. This number would have provided 90% power to detect an improvement in two year survival from the second-look procedure from 25% to 55% at α=0.05. The protocol stated that for the trial to be stopped prematurely very stringent levels of significance ($p<0.001$) would be used.

After potentially curative surgery for colorectal cancer, all eligible patients were to be monitored identically using conventional clinical follow-up together with regular CEA assay, performed centrally. Clinicians would not be informed of the result. When a 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm, the clinician would immediately be informed of the CEA rise so that the patient could be urgently screened to exclude widespread metastatic disease or a non-malignant cause for the CEA rise. If neither was found, and the patient was medically fit for operation, second-look surgery to locate and remove any treatable recurrence was mandatory. In the case of patients in the 'Conventional' arm, the clinician would not be informed of the 'significant' CEA rise nor of subsequent randomisation to not have the CEA rise revealed.

The CEA trial design was devised so that clinical follow-up would remain unbiased, and allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent colorectal cancer. The primary outcome was survival based on death certification through the Office of Population Censuses and Surveys (OPCS) (now called the Office of National Statistics (ONS)). No subset analyses were planned.

The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical Trials Centre at King's College Hospital. CEA assays were performed using a radioimmunoassay technique at a single centre at Charing Cross Hospital.

The intention as stated in the protocol was that the trial would produce:

a) a definitive answer concerning the effectiveness of CEA-prompted second-look surgery to improve survival
b) an accurate picture of the 'lead time' produced by CEA compared to clinically indicated second-look surgery
c) further data relating CEA levels to tumour histology and topography, and
d) a large data base on the natural history of colorectal cancer.[4]

The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements give no indication as to the precise nature of analyses that might follow and are regarded as opportunities for explanatory subset analyses which were not in the event carried out.

Methods: the conduct of the trial 1982 to 1993

Selection of patients

All patients up to the age of 76 who had undergone a potentially curative resection for adenocarcinoma of the colon or rectum, who were fit and willing to adhere to the post-operative monitoring routine were eligible for the study. After the patient had given informed consent, the surgeon was required to take any action considered necessary to detect the presence of synchronous colorectal tumours (both benign and malignant) and to exclude occult liver spread; usually by performing barium enema examination and ultrasound or CT scan of the liver. In addition, chronic lung disease, cirrhosis, chronic pancreatitis, and chronic renal failure, all of which can give raised CEA levels in the absence of recurrent colorectal cancer were excluded by clinical questioning, chest x-ray, liver function tests, blood urea and electrolytes. Smoking habits and alcohol consumption were recorded as heavy smoking or drinking, or a change in these habits, can influence CEA levels.

Patients were excluded if there was evidence of incurable distant spread, either pre-operatively or during the primary operation, or if the CEA level failed to return to the normal range (<10 ng/ml) within six weeks of primary surgery. Patients who had previously received treatment for other types of cancer, apart from basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix adequately cone biopsied, were excluded from the study.

Management of the primary tumour

It was a basic principle that the trial should in no way influence or interfere with the participating surgeon's practise and management of the primary disease. The surgeon was, therefore, at liberty to use any operative technique and to employ peri-, or post-operative radiotherapy, or adjuvant chemotherapy as was seen fit. All that was asked of the surgeon was that to remain consistent as to the treatment used for any particular type of disease.

Patient Entry

A pre-operative blood sample for CEA assay was taken from all patients with suspected colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. Entry to the trial required potentially curative resection of the primary tumour. If at laparotomy, a potentially curative resection was performed and subsequent histology confirmed the diagnosis of adenocarcinoma, the patient was given a full explanation of the study and could be registered.

Figure 3: Trial flow diagram

Monitoring of Patients

Clinical follow-up of all patients continued in an identical manner (three monthly for the first two years and six monthly for the next three years) whilst blood for CEA assay was drawn monthly for the first three years and three monthly for the next two years. If the patient remained well and the CEA was within normal limits as defined by a pre-tested algorithm the monitoring continued according to the schedule.

CEA assay

Ten mls of whole blood were taken from each patient at monthly intervals for the first three years and at three monthly intervals for the next two. The serum was separated and sent to the Trials Centre in special plastic phials. Having logged the receipt of the sample, the trial's secretariat forwarded them in batches, two or three times weekly, to the Medical Oncology Department at Charing Cross Hospital for assay. The results were returned to the Trials Centre for recording and action if appropriate. This centralised system was to ensure that all participating clinicians were kept blind as to the CEA results for all trial patients. It also

ensured quality control of the CEA assay as there was no possibility of inter-laboratory variation.

Serum CEA values were measured by double antibody radioimmunoassay.[31-33] A bank of serum samples has been retained at -20°C.

Throughout the trial the compliance with the regular blood sampling was monitored by the secretariat. Clinicians were reminded each month of the patients for whom samples were due; those who had missed the previous visit were highlighted as urgent. The percentage compliance for each participating patient was calculated as the number of samples received divided by those expected (12 or 13 per year depending on whether the phlebotomy was being done at 4 weekly or monthly visits) x 100. The median time between samples was also calculated. Failure to achieve 50% or less of the expected samples has been defined as poor compliance; the sensitivity to detect CEA rises in this group was greatly reduced and such patients were excluded from randomisation.

The objective of the trial was to compare conventional care in the UK during the period of the trial and an identical policy but with the addition of CEA monitoring and second-look laparotomy for the management of any recurrent disease detected.

Clinicians managing patients under the 'Conventional' policy were totally blind to the results of individual CEA assays. In designing the study, there was an inevitable compromise between employing CEA to its maximum advantage, by requesting an immediate repeat sample from any patient demonstrating a rise, and the essential blinding component, which did not allow for the request of additional samples. The design allowed only routine monitoring of CEA thus keeping all clinicians blind until after the randomisation for 'Aggressive' arm patients and completely for all others.

'Significant' Rises in CEA

If a 'significant' rise in CEA occurred, the record of the patient was reviewed at the Trials Centre and provided no evidence of suspected colorectal or other disease was recorded in the CRF, the patient was randomised either into an 'Aggressive' or 'Conventional' arm. A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on two successive occasions and one of the following conditions was also met: the CEA level was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the highest value was more than 7ng/ml above the lowest value ever recorded.

Figure 4: CEA algorithm

Randomisation

For a patient to be randomised, compliance with the blood monitoring regimen had to be greater than 50% over the preceding nine months. Patients whose compliance was between 50 and 70% or whose immediate post-operative sample had not been received within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was also stratified by participating clinician. A block size of two was used in order to maintain as close a balance as possible between the two treatment arms. Clinicians were not only totally blind to half the randomisations (i.e. those in the 'Conventional' arm) but also to the assay values and hence the prospect of randomisation, prediction of the following allocation was not possible.

If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise immediately by telephone from the trial centre and subsequently in writing and was requested to contact the patient urgently, and with the patient's permission, carry out a full clinical work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g., change in smoking or drinking habit) and also to identify if present, distant incurable spread. In the absence of these conditions the surgeon was requested to undertake a mini-laparotomy proceeding to a full laparotomy with macroscopic clearance of disease should this be possible. Prior to surgery patients were made fully aware of the situation including the fact that they had been randomised within the trial to undergo a second-look procedure. This was only undertaken if the patient gave informed consent.

For patients randomised to the 'Conventional' arm no further action was taken; the clinician was not informed that the CEA had risen nor that the patient had been randomised.

If at any stage a patient in the study developed clinical evidence of recurrent disease the clinician was at liberty to manage the patient according to usual practice. If the disease was in the abdomen and was thought to be treatable by a second-look operation with re-resection, this was perfectly acceptable. The clinician was blind as to whether such patients had been randomised to the 'Conventional' arm of the trial or had not been randomised because the CEA had failed to denote the presence of recurrent disease.

Second-Look Laparotomy

The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was detected all that was required prior to closure, was biopsy. Otherwise following a full excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis was undertaken. The liver was fully mobilised to determine whether any tumour was present. Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then carried out with the objective of total extirpation of all recurrence. Complete data recording of the procedure along with the results of the histology of all potentially involved sites was required by the trial's office.

For patients in whom a radical resection was achieved after second-look surgery (motivated either on clinical information or because the patient had been randomised to the 'Aggressive' arm) the follow-up schedules for clinical examination and blood sampling reverted to those following the primary operation. However, for the randomised patients, the 'Aggressive' policy was maintained in that clinicians were immediately notified of any CEA levels above 10ng/ml.

Death

Every patient registered onto the study was 'flagged' with the Office of Population Censuses and Surveys (OPCS) who provide automatic notification of date of death allowed the trial centre to receive minimum information on death for all patients.

Statistical Analysis

The study was specifically designed with late randomisation in order to maximise statistical power. It was originally intended to recruit 2,000 patients with the anticipation that about 25% would show a CEA rise as the first evidence of possible recurrence. This number would have provided 90% power to detect an improvement in two year survival from the second-

look procedure of 55% (i.e. from 25% to 55%) at α=0.05. The protocol stated that for the trial to be stopped prematurely very stringent levels of significance ($p<0.001$) would be used.

A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not entering patients into the trial was asked to review the data after the first 100 patients had been randomised, which occurred in January 1988, and again after 200 patients had been randomised in February 1993, at which point it was recommended that the trial was stopped since it was very unlikely that any clinically important advantage would be demonstrated for patients undergoing second-look surgery.

Methods of the RIAT process

The data

The RIAT restorative authors had been warned by the statisticians called in to look at the data in 2003-4 that "the databases were corrupted with key variables no longer abstractable" and that they could not be analysed without a lot of work.[34;35] We found that the data on paper and on file was accessible and we had no reason to doubt the veracity of individual items. The problem we found was that the electronic files had numerous problems with format which made the files on the 1447 individual patients difficult to handle but that the data entries were not themselves corrupted.

One of the RIAT restorative authors (KM) had worked in the trials unit(s) during the time the CEA Trial data were being accrued and knew the systems in use and their changes but was not directly involved in this trial at any stage.

The data problems encountered and resolved were as follows:

- The codes that indicated that a patient had met the criteria for CEA elevation and then whether randomly allocated to 'active' or 'Conventional' were preserved and tallied with the number in the 1994 manuscript.[15]

- There were variations in the way dates were recorded in the database. There had been migrations of data from a Prime server using 'Universe' to Excel and the interpretation of the present authors, with information from contemporary witnesses was that in undertaking the task operators did not always correctly specify these data as 'dates' when importing, and/or allowed them to be converted to American date formats. These errors prevented calculations and would have defeated running a survival analysis without correction. The dates were however visually readable and not 'corrupt'. Some could be corrected by running current versions of software. Others were manually corrected by re-entering them in a Microsoft date format. Paper records were available to resolve uncertainties.

- The next problem was in linking these three groups of patients (randomised to 'aggressive', randomised to 'Conventional' and not randomised) to the dates for survival analysis. Individual patients were uniquely identified in the files by seven digit strings. To these had been added letters at the beginning and end of the strings flagging them for trial administrators' checklists and perhaps for subgroup analysis. Once the problem was identified, and we had established that the initial and terminal letters were redundant for analysis of the primary endpoint, it was a straightforward matter, in expert hands, to write code to restore the seven digit strings.

- It was evident that the seven digits did not represent a simple sequence but certain positions identified particular centres. We then recognised a consistent pattern of mismatch. The fourth digit differed systematically so what was a zero in one file was an 8 in the other with all other digits remaining the same. It was suggested to us that the fourth digit replacement was used to identify patients suitable for *post hoc* subgroup analyses but no documentation was found to confirm this. By checking back to the dates of birth we were able to confirm that this systematic correction resolved the problem and most of the data were then usable.

- By ranking all the data in the paired files for line by line visual inspection residual discrepancies were identified. Scrutinising the digit strings allowed for seven of the remaining eight pairs to be reconciled and verified on dates of birth. We failed to resolve only one out of 1447 records in each file.

- Inspection of the accrual of death dates was discontinuous for a couple of years suggesting a lapse in either recovery or entry. The current trials centre obtained permission to re-run the Office of National Statistics (ONS) search in July 2012.

It should be remembered that the data collection ran from 1982 to 1993 during which time there was a multiplicity of operating systems, disc drives and software. Nevertheless we had electronic files in Microsoft excel spread sheets in recognisable formats. We identified several problems but they were systematic and not random (we would not use the value laden word 'corrupted'). We were able to rectify the formatting errors and verify that the data used for our analysis were correct. The Kaplan Meier analysis was re-run.

Results

The study opened to recruitment in November 1982 and was closed by the Working Party, on the acceptance of a recommendation from the Data Monitoring Sub-committee, on 17th February 1993. During this period 1,447 patients were registered by 73 participating clinicians in 58 hospitals in the United Kingdom and Europe. Of these 39 (2.7%) were deemed ineligible since their CEA did not fall below 10 ng/ml by six weeks after surgery. A further 173 patients were excluded from analysis; four did not have a confirmed diagnosis of adenocarcinoma, 6 were considered unfit for continued monitoring, 4 had a previous and 1 a simultaneous non-colorectal malignancy, 2 had metastatic disease, and 156 (10.8%) although apparently willing never complied with the requirement for monthly blood sampling or only did so for 3 months or less.

Figure 5

In the 1,235 patients who continued in the trial, 80% achieved a greater than 60% compliance with blood sampling; whilst 12.5% registered between 40-59% of the required samples and only 7.5% had compliance of less than 40% The majority of randomisations (160/216; 74%) were prior to the second anniversary of the primary diagnosis. Three patients randomised had prior recurrent (2) or metachronous (1) disease detected clinically, without a rise in CEA and were operated upon.

Two hundred and sixteen patients developed a 'significant' rise in CEA and as no recurrent disease had been recorded at their latest trial follow-up, they were randomised by the Trial

Office (108 to each arm). The median time from primary surgery to randomisation was 403 days, (range 103 to 1754) with no statistical difference between the two groups.[15]

The characteristics of patients in the two groups are given in Table 1.

Table 1

	Aggressive N=108	Conventional N=108
Sex male (%)	60(56%)	68(63%)
Age years, median and range	64 (33-75)	62 (35-75)
Pathological stage	N(%)	N(%)
Dukes' A	5 (4.6)	5 (4.6)
Dukes' B	46 (42.6)	49 (45.4)
Dukes' C^1	36 (33.3)	38 (35.2)
Dukes' C^2	17 (15.7)	10 (9.3)
Missing	4 (3.7)	6 (5.6)

The stage mix of 980 patients who were eligible for inclusion in the randomised trial but who did not have a CEA rise as defined was Dukes' A 15.1%, B 55.2%, C1 23.3%, C2 6.4%.

Of the patients randomised to the 'Aggressive' arm 83 (77%) had recurrent cancer identified and 62 (57%) patients had 'second-look' surgery. In patients randomised to the 'Conventional' arm 89 (82%) had developed recurrent disease by the date of analysis. In these 26 (24%) second-look procedures were undertaken. By February 1993, 88/108 patients had died in the 'Conventional' arm compared with 91/108 in the 'Aggressive arm'. The hazard ratio was 0.84 (95% confidence intervals 0.62-1.13; P=0.25).[15] It was considered by the data monitoring committee to be "highly unlikely that any survival advantage would be demonstrated for patients undergoing second-look surgery". This was communicated to the trial centre.

The data were restored by the RIAT authors for 1446 of 1447 patients to the extent that the RIAT authors were confident of their dates of birth, death and whether they met criteria for entry into the controlled trial and then to which arm they were allocated.

The electronic records were intact with respect to the identity of the patients, which patients had reached the criteria for randomisation, and the trial arm to which they had been randomly allocated for all 216 patients who were randomised. The sex, age, primary site and Dukes' stage as recorded in the 1994 manuscript are shown in Table 1.

Certification of death were obtained from ONS on behalf of the RIAT restorative authors for 102/108 patients in the "Aggressive" arm from 17/10/1983 to 06/01/2010 and in 102/108 patients in the "Conventional" arm from 19/09/1984 to 08/09/2011. We also have dates of death in 862 of the 1230 patients who were not randomised. Kaplan Meier analysis in these three groups is shown in Figure 5.

Figure 6 Kaplan Meier analysis

The lead time conferred by CEA monitoring, defined as the median time to clinically detected disease for patients randomised to the 'Conventional' arm, was 323 days (SE 60; 95% confidence interval (CI) 203-443). This is expressed visually (Figure 6) as an analysis of time to confirmed recurrent disease in the randomised patients according to their therapeutic arm. This analysis included censored observations on 23 patients, however only five of these had a censored time less than the lead time. It was regarded as unlikely, therefore, that the lead time would decrease as further events occur. The analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs 70% at a year.

Figure 7 Lead time.

Discussion

We have restored data sufficient to achieve the primary outcome of interest as specified by the CEA trialists:

> "Does a policy of CEA-prompted second-look surgery following 'curative' resection of colorectal cancer produce a decrease in morbidity and mortality due to tumour recurrence, despite sequelae of second look surgery?"

The answer is that detecting and acting on CEA elevation did not reduce mortality. That finding led to the closing of the trial in 1994[6;7] and we confirm it here. There was small non-significant excess of deaths in the 'Aggressive' arm. The burden of morbidity attributable to the greater number of investigations and operations was not captured by the trial protocol.

The second planned analysis was to obtain an accurate picture of the 'lead time' produced by CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up patients considerably sooner than the clinical methods available at the time by about six months to a year.

Use of CEA is currently used by some for this purpose but in development of the PulMiCC trial we found variability in its use and inconsistency in the threshold used.[14] Other methods of investigation (MRI, PET and improved CT and echo) are now used to detect recurrence before it is clinically evident. It cannot be presumed, and on the basis of the CEA Second-Look Trial results there is doubt, as to whether earlier detection leading to further surgery, leads to better outcomes.

The third and fourth intentions set out by the CEA trialists were c)to obtain further data relating CEA levels to tumour histology and topography and d) a large data base on the natural history of colorectal cancer.

Multiple CEA assay results exist in the data we hold for 1446 patients which could now be linked to survival as a result of the RIAT restorative work. The opportunity for further analysis exists and an approach for access to these data been received.

With respect to the natural history of colorectal cancer although we trust the death certification data for the date of death it has been shown that "at least a third of all death certificates are likely to be incorrect"[36]. No doubt aware of this and seeking much more detailed information, the CEA Trialists asked for detailed post-mortem examinations many of

which are in the trial documents. Given the many differences in cancer evaluation and imaging in the intervening thirty years we would be cautious about their value now. Furthermore it appears that it was disagreement concerning explanatory analyses which contributed to failure to publishing the primary outcome of interest.[15] The purpose of such analyses is to discover subsets of patients in whom there was a benefit from the intervention under evaluation and to thus determine the characteristics of patients in whom the intervention might have had a beneficial effect by analysis of mediators and moderators.[37] There is a general objection to this exercise because it can lead to spurious associations.[38;39] Furthermore when there is no overall benefit found, as in the CEA Second-Look Trial, any subgroup(s) where there is a positive association between intervention and outcome, must be balanced by one or more other groups where there was net harm. There were no completed subset analyses in 1994 and we have not attempted any in restoring the trial.

The answer to the primary research question was clear in 1993 and was the explicit reason for stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery had been missed and in the absence of benefit there was net harm being done to the patients. We cannot say whether this is an inevitability associated with any form of second-look surgery for colorectal cancer and that these findings of the CEA Trials will apply to any other means of selecting patients for second-look surgery. The forms of second look surgery now widely practiced in colorectal cancer are liver and lung resection of metastases.

- Full mobilisation of the liver at second-look laparotomy was included in the CEA Trial protocol. Hepatic resection has entered routine practice based on observational data[40] and an opportunity to do a randomised trial, for which a power calculation was proposed in 1992 from the Mayo Clinic[41] was not taken.[8]
- Two patients had a thoracotomy prompted by CEA elevation. Pulmonary metastasectomy for colorectal cancer is, after primary lung cancer, the second commonest thoracic cancer operation and id the subject of an ongoing randomised controlled trial.[42]

If the CEA Trial findings result can be generalised, and there is no obvious reason in principle why they should not be, it would suggest that more critical scrutiny of the evidence base used to bring surgery into practice is justified. The CEA Trial was a well conceived and meticulously executed randomised trial and we hope that publishing it now more than twenty years after its completion will indicated the possibility of more randomised trials in surgery.[43]

Legends

Figure 1. The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.[4]

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]

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Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from ONS statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230) Some would have had clinically evident early recurrence precluding randomisation. The initial plateau is an illustration of a death free interval[44] or "immortal time bias"[45] Patients in prospective studies may have a built in obligatory survival time from some starting point in order to attain the requirements to be included in the data set. This is an artefact but may be absorbed into survival time adding to and not readily distinguished from survival time attributed to treatment.

Figure 7. Illustration kindly provided by JMAN which was as used by him in presentations related to the analysis of the DMC in 1993. We have not verified the dates of detection but there is no reason to doubt them and it remains a valid illustration of the efficacy of CEA monitoring I detecting recurrence but does not alter the conclusion that second-look surgery prompted by it is ineffective in improving survival.

All authors have completed or will complete the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributor statement

TT instigated the recovery of the data, worked on the database recovery described in the manuscript and wrote the first and edited the final version of the manuscript.
KM navigated the data files and worked on the database recovery described in the manuscript.
FF performed the analysis of the recovered data and the presentation of the analysis.
RCGR negotiated access to the data and with TT contacted and interviewed the members of the original trial team.
All authors have read and contributed to successive iterations of the manuscript and approve the submitted version.

Data sharing

We are prepared to share the data in our possession and to direct any applicants for stored data to the head of the trial centre where the data are still held.

Acknowledgments

We have agreed with the CEA Trialists that the RIAT restorative authors intend to fully acknowledged them (which they all welcomed) but that their individual inclusion and its wording could await a better idea of where and how this will appear. No members of the present Trial Centre (as we understand it) had any involvement with the CEA trial and while we will wish to acknowledge access to data we are not yet sure exactly what form this will take.

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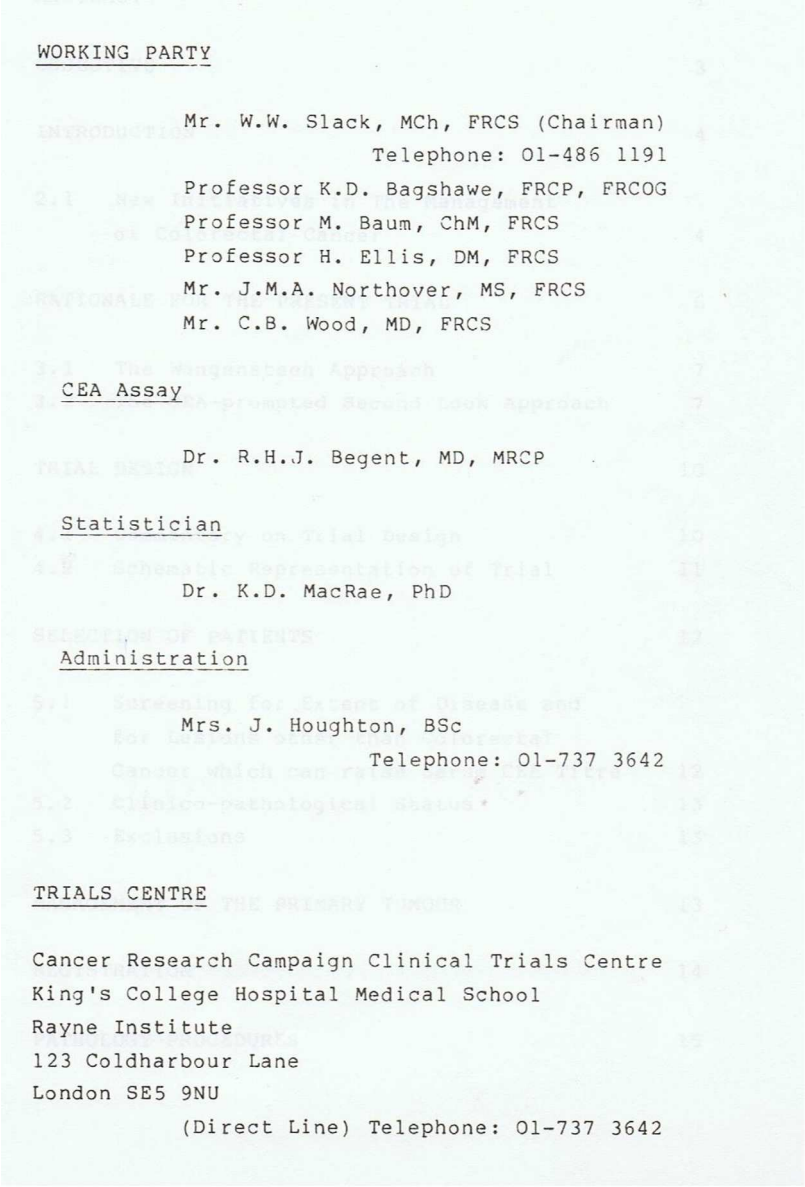

WORKING PARTY

Mr. W.W. Slack, MCh, FRCS (Chairman)
Telephone: 01-486 1191
Professor K.D. Bagshawe, FRCP, FRCOG
Professor M. Baum, ChM, FRCS
Professor H. Ellis, DM, FRCS
Mr. J.M.A. Northover, MS, FRCS
Mr. C.B. Wood, MD, FRCS

CEA Assay

Dr. R.H.J. Begent, MD, MRCP

Statistician

Dr. K.D. MacRae, PhD

Administration

Mrs. J. Houghton, BSc
Telephone: 01-737 3642

TRIALS CENTRE

Cancer Research Campaign Clinical Trials Centre
King's College Hospital Medical School
Rayne Institute
123 Coldharbour Lane
London SE5 9NU
(Direct Line) Telephone: 01-737 3642

Figure 1. The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.[4]
152x227mm (200 x 200 DPI)

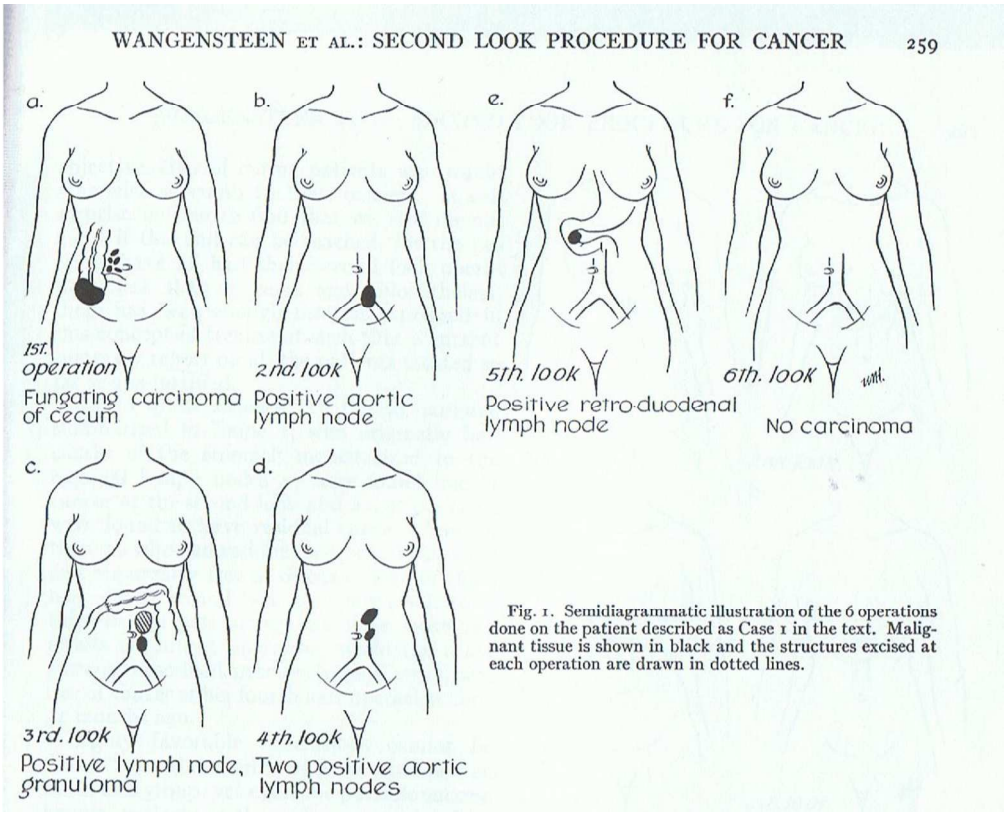

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]
161x130mm (200 x 200 DPI)

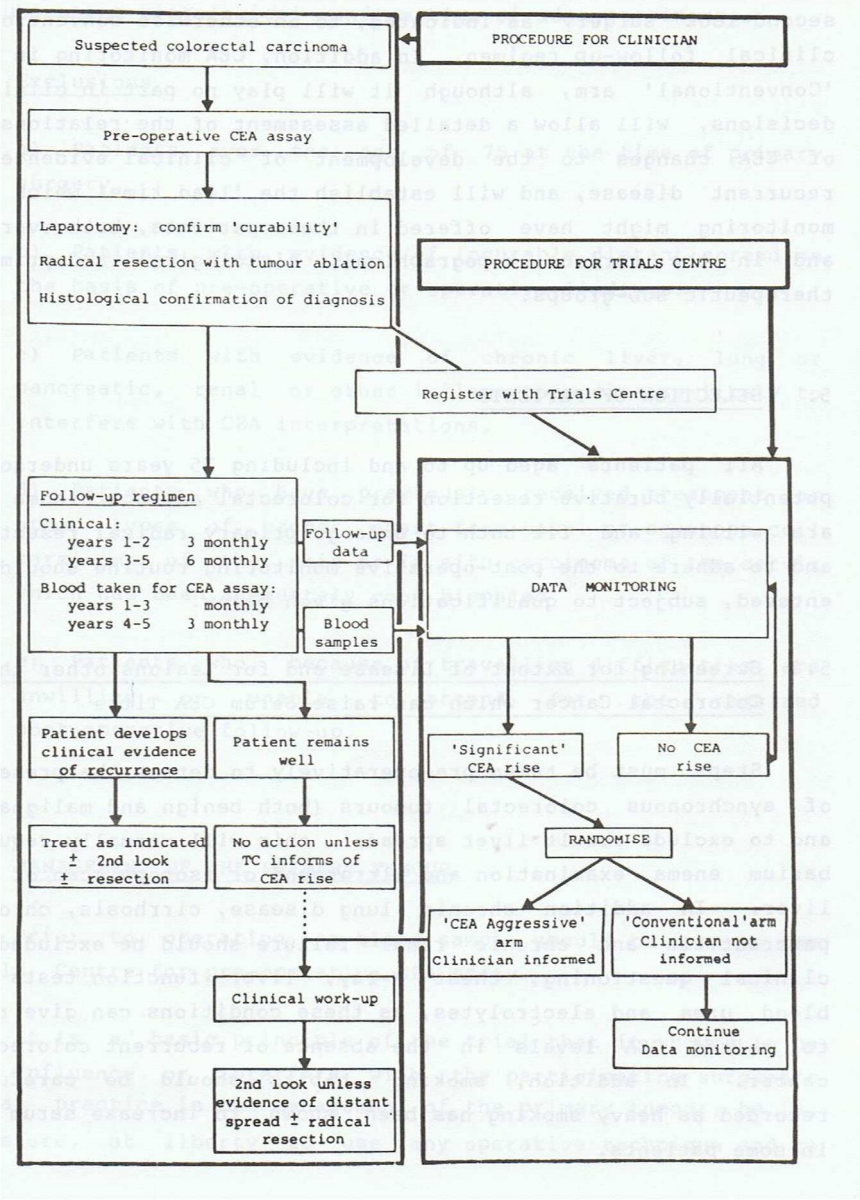

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]
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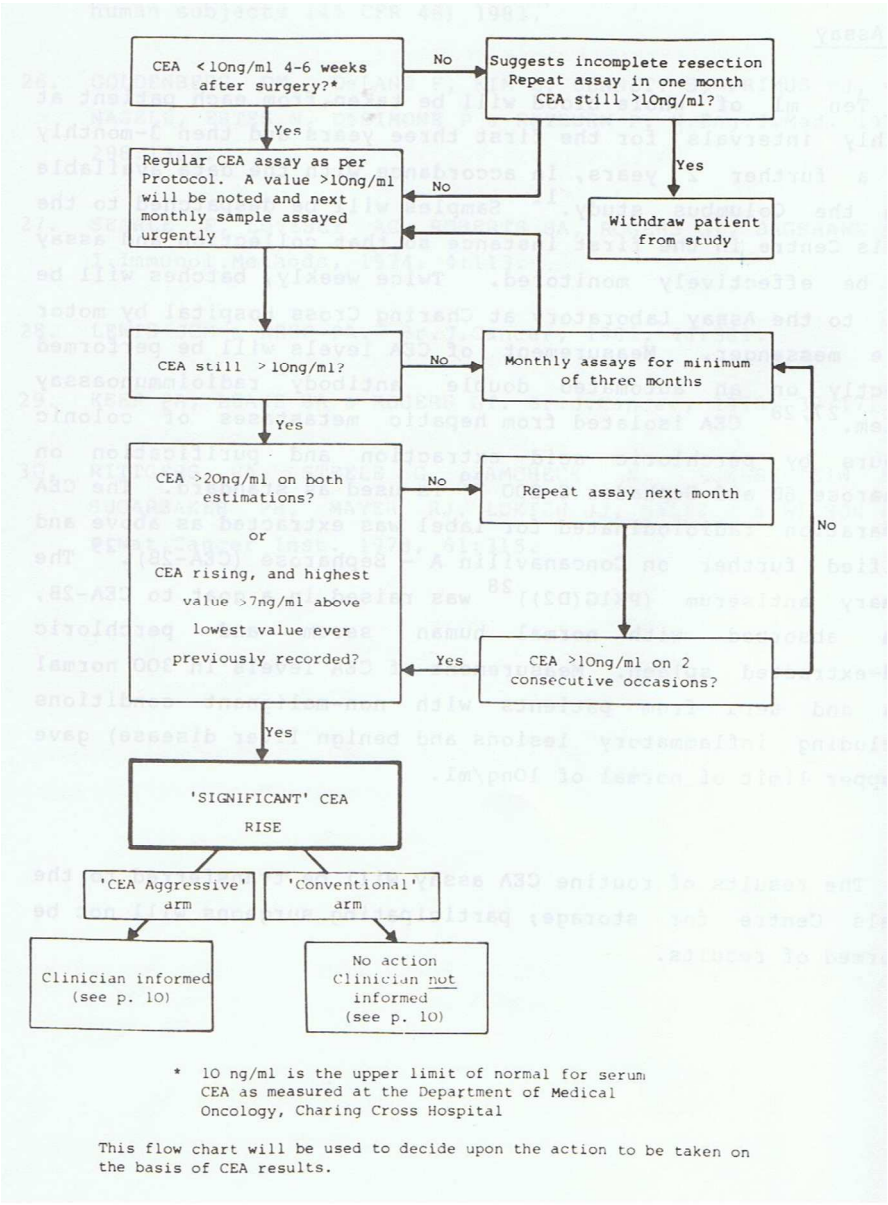
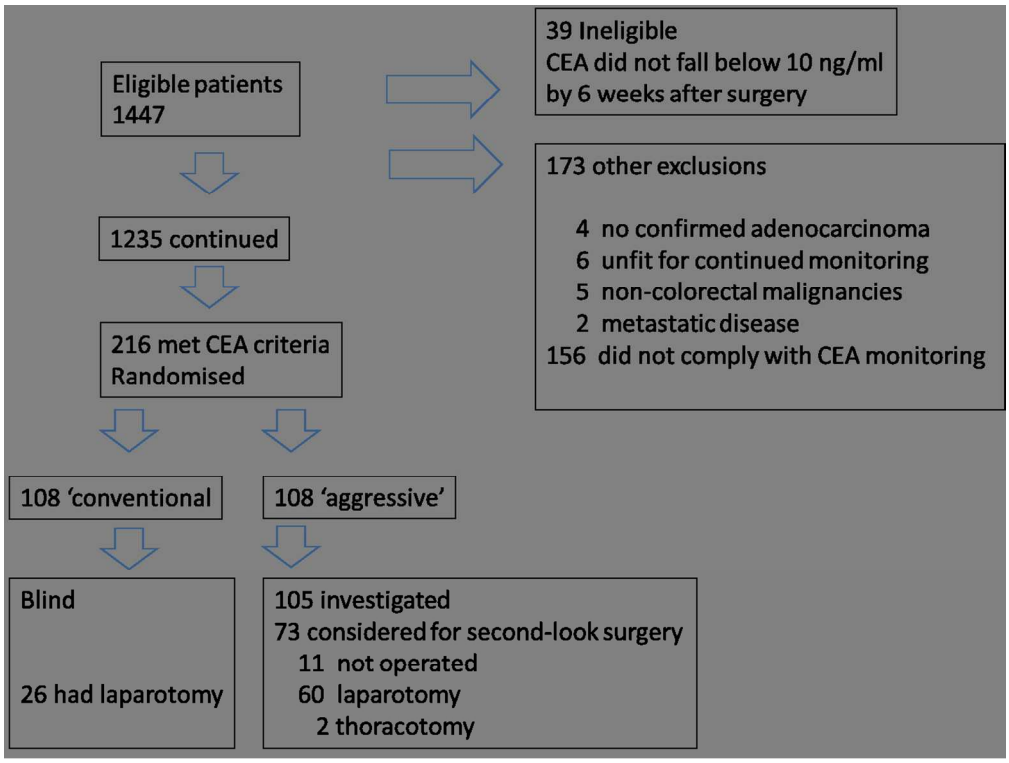


Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22]
159x215mm (200 x 200 DPI)



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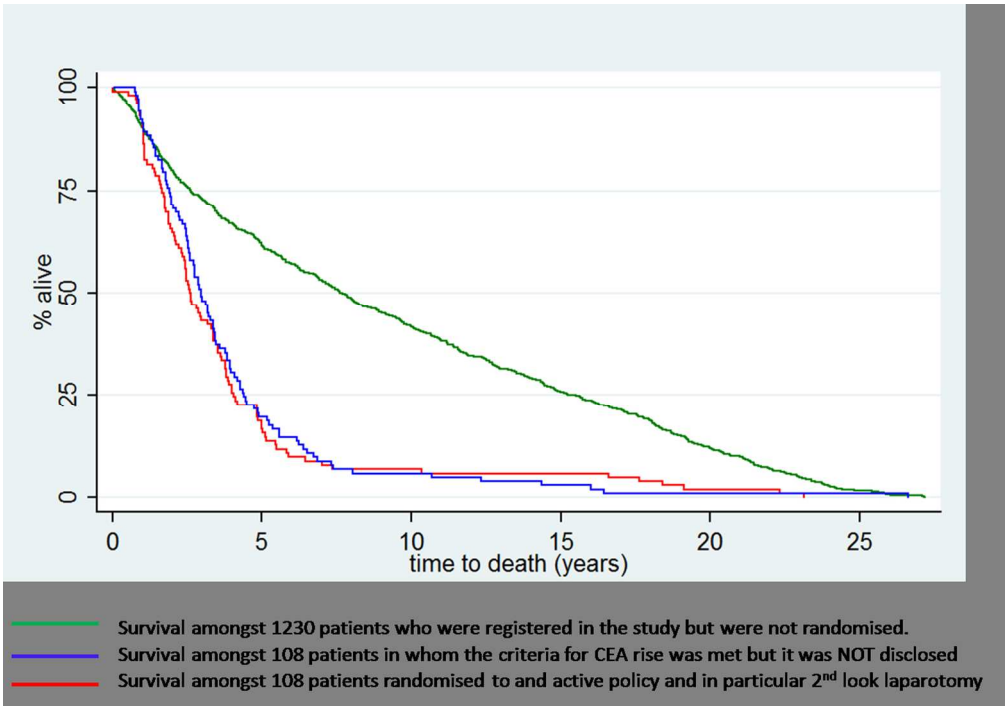

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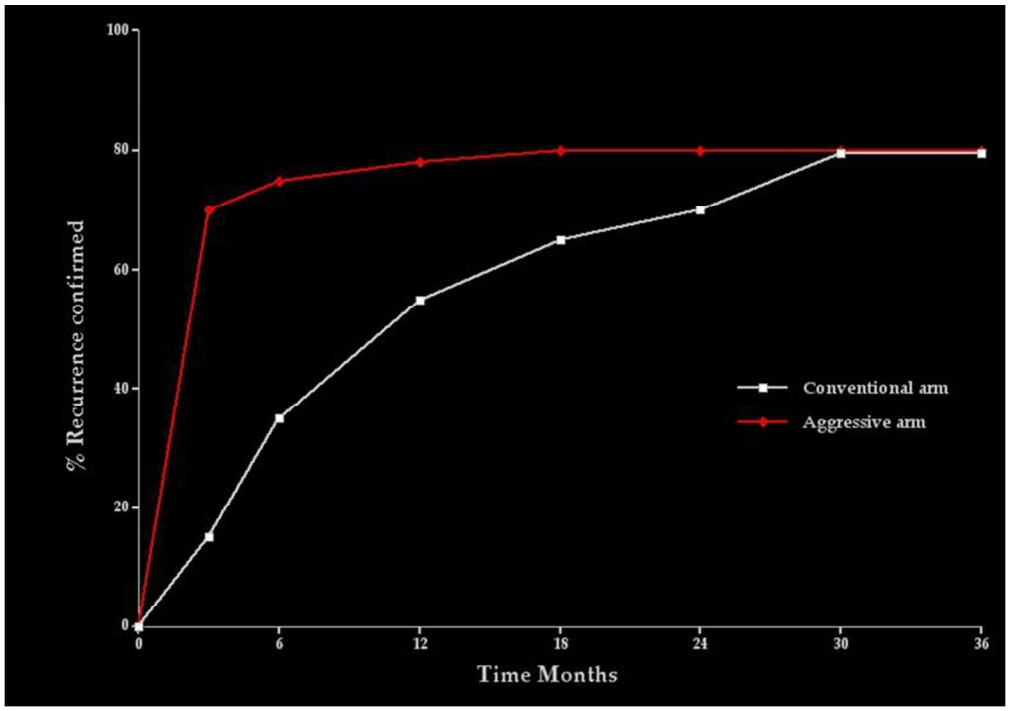

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194x136mm (104 x 104 DPI)

RIAT Audit Record (RIATAR)

*A tool for documenting the transformation from regulatory documents to journal publication, based on the CONSORT 2010 checklist of information to include when reporting a randomised trial**

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
Title and abstract						
	1a	Identification as a randomised trial in the title	1	Cover	1	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3	1-2	None written	
Introduction						
Background and objectives	2a	Scientific background and explanation of rationale	5-6	4-9	None written	
	2b	Specific objectives or hypotheses	3	2	2	
Methods						
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	10-11	2	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	None	None	None	
Participants	4a	Eligibility criteria for participants	7-8	12-13	2-3	
	4b	Settings and locations where the data were collected	12	Not stated	Not stated CEA assays 4	This was of course implicit that these were in units performing colorectal cancer

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
						surgery within hospitals
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10	16,18	4, 6-7	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed. NOTE “lead time” was a planned analysis There was also reference to “parallel studies”	7	2 21	7	I cannot see that this was explicitly stated in current terminology but it was all cause mortality and that is implicit throughout and not in doubt.
	6b	Any changes to trial outcomes after the trial commenced, with reasons	None	None	None	
Sample size	7a	How sample size was determined	10-11	19	7	Lacks clarity and 2000 suggests a degree of “ballpark” but it is there.
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10-11	19	7-8	
Randomisation:						
Sequence generation	8a	Method used to generate the random allocation sequence	9		5	
	8b	Type of randomisation; details of any	9		5	This is not very

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
		restriction (such as blocking and block size)				detailed but is all we found.
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9-10		5-6	This was dealt with in some detail in the 1994 manuscript.
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10			Patients were enrolled by participating clinicians and it is quite clear that it was the trial centre that randomised.
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	10			
	11b	If relevant, description of the similarity of interventions				
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13			
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A			
Results						
Participant flow	13a	For each group, the numbers of	12-13		9	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
(a diagram is strongly recommended)		participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome				
	13b	For each group, losses and exclusions after randomisation, together with reasons	13 Lines 506-10 are the restorative analysis		None recorded	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12		9	
	14b	Why the trial ended or was stopped	12		9	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13		17	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12 12 13		11	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Survival 13 Lead time 14		10 9	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended				
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory				

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not dealt with			I don't think the data are good enough to document these and they are implicit in the stopping decision. They could be discussed if required.
Discussion						
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14			
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15			
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15			
Other information						
Registration	23	Registration number and name of trial registry				
Protocol	24	Where the full trial protocol can be accessed, if available	UCL			
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	None		CRC	

* The aim of this audit tool is provide a permanent record of the parts of text, tables and figures of the source Clinical Study Report (CSR) selected for inclusion into the RIAT manuscript submitted for publication. This tool is based upon checklist items described in the CONSORT 2010 statement, which is a widely adopted standard for reporting randomised trials. RIAT authors should consult the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. Similar audit records can be created for other types of trials by adapting other CONSORT extensions, e.g. for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. See www.consort-statement.org for more details.

BMJ open

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

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Manuscript ID:	bmjopen-2013-004385.R1
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Date Submitted by the Author:	06-Feb-2014
Complete List of Authors:	Treasure, Tom; UCL, CORU Mathematics Monson, Kathryn; University of Sussex, Sussex Health Outcomes, Research & Education in Cancer (SHORE-C) University of Sussex Fiorentino, Francesca; Imperical College London, Cardiac Surgery Russell, Christopher
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Colorectal surgery < SURGERY, Chemical pathology < PATHOLOGY, Adult oncology < ONCOLOGY, Adult gastroenterology < GASTROENTEROLOGY, CHEMICAL PATHOLOGY
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
RIAT for public access.zip	

Title

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

Tom Treasure[1]
Kathryn Monson[2]
Francesca Fiorentino[3]
Christopher Russell

[1]Clinical Operational Research Unit, University College London

[2] Sussex Health Outcomes, Research & Education in Cancer (SHORE-C)
University of Sussex

[3] Department of Cardiothoracic Surgery, NHLI, Imperial College London

All authors have completed or will complete the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributor statement

TT instigated the recovery of the data, worked on the database recovery described in the manuscript and wrote the first and edited the final version of the manuscript.
KM navigated the data files and worked on the database recovery described in the manuscript.
FF performed the analysis of the recovered data and the presentation of the analysis.
RCGR negotiated access to the data and with TT contacted and interviewed the members of the original trial team.
All authors have read and contributed to successive iterations of the manuscript and approve the submitted version.

Data sharing

We are prepared to share the data in our possession and to direct any applicants for stored data to the head of the trial centre where the data are still held.

Acknowledgments

The RIAT authors are grateful to Jonathan Ledermann, Director of the Cancer Research UK & UCL Cancer Trials Centre, University College London, (where the CEA files were stored) and Sharon Forsyth for her assistance in accessing the CEA trial data and updating the Office of National Statistics records for death registration. The RIAT authors also met with the following persons who were members of the 1982 Working Party at the Cancer Research Campaign Clinical Trials Centre (CRC CTC) King's College Hospital Medical School, London and/or were listed as contributors in the 1994 manuscript from the CRC CTC at the Rayne Institute, 123 Coldharbour Lane, London SE5 9NU: M Baum, RHJ Begent, H Ellis, J Houghton, M Irving, CA Lennon, JMA Northover, WW Slack and CB Wood. We are

grateful to them for frank discussions concerning the progress of the study and the factors leading to its abandonment.

FF is partly funded by the British Heart Foundation.

None of the authors has a conflicts of interest.

Abstract

Objectives: in patients who have undergone a potentially curative resection of colorectal cancer does a 'second-look' operation to resect recurrence, prompted by monthly monitoring of carcinoembryonic antigen, confer a survival benefit?

Design: randomised controlled trial

Setting: 58 hospitals in the United Kingdom and Europe.

Participants: from 1982 to 1993, 1447 patients were enrolled. Of these 216 met the criteria for CEA elevation and were randomised to 'Aggressive' or 'Conventional' arms.

Interventions: 'second-look' surgery with intention to remove any recurrence discovered.

Primary outcome measure: survival.

Results: by February 1993, 91/108 patients had died in the 'Aggressive arm' and 88/108 in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37). By 2011 a further 25 randomised patients had died. Kaplan Meier analysis showed no difference in long-term survival.

Conclusions: the trial was closed in 1993 following a recommendation from the Data Monitoring Committee that it was highly unlikely that any survival advantage would be demonstrated for CEA prompted second-look surgery. This conclusion was confirmed by repeat analysis after twenty years.

Strengths and limitations of this study

- The CEA Second-Look Trial was a well-planned and carefully executed study with a clear question and a well-defined outcome of interest.
- Second-look surgery prompted by the best available indicator of recurrence at the time conferred no survival advantage.
- A further strength, and a reason to publish this trial now, is that it shows that randomised trials in surgery can be done and that the result may be contrary to the beliefs and expectations of practitioners based on their uncontrolled observations.
- A limitation is that present day means of detection, based on imaging and anatomical localisation, may detect patients with recurrence curable by surgery. It follows that the effectiveness of second-look surgery prompted by new imaging methods cannot be assumed but should be the subject of controlled trials.

Introduction

It was observed during the 1970s that the outlook for patients with colorectal cancer was not good. Only one in four patients survived for five years after diagnosis and radical surgerywas observed to be curative in under half of patients (1). Results had not improved in several decades.(2-4). Refinements in primary operative techniques had not made a difference(5) and it was considered unlikely that technical modifications would lead to improvement in survival following surgery.(1;2) Routine surgical follow-up had not led to further surgery being shown to be beneficial. Clinical evidence of recurrence usually meant that the tumour would be unresectable at second-look laparotomy(6) First-hand experience of members of the Carcinoembryonic antigen (CEA) Second-Look Trial development group was that of 180 patients, followed up from six months to 15 years, at a total of 2319 out-patient clinic visits, only one patient could be considered to have had a potentially curative second-look operation. (7) To re-resect with prospect of benefit, recurrence had to be detected before it was clinically evident(4) but more pro-active clinical follow-up of asymptomatic patients by three monthly sigmoidoscopy, barium enema and chest X-ray (the methods available at the time) had failed to show improvement in 5-year survival.(8) Nevertheless, there had been several reports of 30% five-year survival in selected patients after radical resection of recurrent cancer(3;9;10) and resection was believed to sometimes lead to "cure".(3;9-11)

Improving detection and treatment of recurrent disease: the context in1982

The trial development group considered the evidence available at the time for methods of detecting recurrence early and a founding principle of the CEA Second-Look Trial was that early detection of recurrent tumour would only be justifiable if further treatment offered the prospect of benefit to the individual patient.(4) The evidence available to the group is outlined below.

The Wangensteen Approach:

During the 1950s the systematic use of a policy-based second operation was reported. Patients at high risk of recurrence (those with Dukes' Stage C tumours) were re-operated on at 6-monthly intervals, resecting recurrence when found, until they were 'tumour free'. If cancer had been found the patients were scheduled for 3rd and more "looks", up to six further abdominal operations, "before the abdomen was free of cancer". Once a patient had undergone a negative laparotomy, no more surgery was recommended. Sixty-four patients with colon or rectal cancer were managed in this way. In 35 (55%) of them the "second-look" laparotomy was negative for the discovery of recurrent cancer, seven of whom subsequently had clinical recurrence. There were four (6%) operative deaths.(12) The CEA trialists concluded that this 'blanket second-look' policy might have produced some "cures" but entailed high rates of negative laparotomy and an unacceptable operative mortality rate.(4)

Figure 2 from Wangensteen 1954

The CEA-prompted Second-Look Approach

CEA had been shown to detect recurrence of colorectal cancer following surgery.(13-18) CEA rose, on average, four months prior to clinical evidence of recurrence(14) and there were reports of the use of serial serum carcinoembryonic antigen (CEA) assays to detect asymptomatic recurrences in the belief that curative resection would be possible more frequently.(13-15) Several groups used CEA in this way, and found low false positive

rates(6;19) and the resectability rate of the recurrence was higher than when clinical criteria were used to prompt re-operation.(6) In the largest published experience of CEA in a post-operative monitoring role(6;13) resectable recurrent tumour was found in 70% in whom re-operation was prompted by a rise in the serum CEA compared with a quarter of patients undergoing second-look laparotomy prompted by clinical indications. Others had not found CEA to be useful in this post-operative monitoring role. Even if efficacy of CEA detected recurrence was accepted, there was also the unresolved question of effectiveness: if more patients were detected and there were more instances of resectable recurrence, did that lead to better survival and patient benefit? The conflicting interpretations of observational data resulted in calls for trials(13;19;20) including within a 1981 NIH Consensus Statement.(18)

The objective of the CEA Second-Look Surgery Trial was to determine whether, following potentially curative primary surgery for colorectal cancer, mortality could be decreased by a policy of second-look surgery prompted by rising serum carcinoembryonic antigen (CEA). The trial ran from 1982 to 1993. The main result, that there was no survival advantage, was reported in 1994 to the British Oncological Association(21) and was published in a letter to the Journal of the American Medical Association.(22)

Surgery for colorectal cancer recurrence has since become routine both in the form of hepatic resection(23) and pulmonary metastasectomy(24) but without evidence from controlled trials for either practice.(25) When doubts were raised about the security of the evidence in the British Medical Journal in 2007(26) a general belief existed that randomised controlled trials of the effectiveness of resection of liver or lung metastases were not possible and were not needed. These paired beliefs are brought into question by the CEA Second-Look Trial: a randomised trial was done and the presumed benefit of surgery for cancer recurrence was not seen.(21;22)

Abandonment of the trial in 1994 and gaining access to the data in 2011

The RIAT restorative authors had been involved in various studies related to surgery for disseminated colorectal cancer(26-28) including a conundrum as to whether discovery of an elevated CEA assay should prompt or be considered a contra-indication to pulmonary metastasectomy.(29) We knew the CEA trial to have been enrolling patients in the 1980s but when we searched the literature for the result of the trial we learned that it had been abandoned in 1994. In 2009 we contacted the chief investigator of the trial and the present director of the unit. The data were initially thought to be irretrievably lost or irrecoverable. However, staff at the trials centre retrieved archived CEA electronic files and the death data were updated. We gained access to anonymised electronic data in 2011. The process of data restoration is described later.

Amongst the documents were listed the members of the trial development group in the 1982 protocol(4) and the contributors to the 1994 manuscript.(30) None of these individuals expressed an interest in resuming work on the trial or were in a position to do so. When we contacted them later to share the restored data with them no one raised any objection but on the contrary encouraged us to publish their findings.

Figure 1 Working Party from the 1982 Protocol

Methods: trial intent and design

The recruitment intentions and the trial protocol as presented here are essentially as written in the manuscript prepared in 1994 with the intention of publishing the trial.(30) The text has been edited by the RIAT authors but no new material has been introduced.

The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years and to follow them for five years. The study was specifically designed with late randomisation in order to maximise statistical power. It was originally intended to recruit 2,000 patients with the anticipation that about 25% would show a CEA rise as the first evidence of possible recurrence. This number would have provided 95% power to detect an improvement in two year survival from the second-look procedure from 25% to 55% at α=0.05. The protocol stated that for the trial to be stopped prematurely very stringent levels of significance ($p<0.001$) would be used.

The CEA trial design was devised so that clinical follow-up would remain unbiased, and allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent colorectal cancer. After potentially curative surgery for colorectal cancer, all eligible patients were to be monitored identically using conventional clinical follow-up together with regular CEA assay, performed centrally. Clinicians would not be informed of the result. When a 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm, the clinician would immediately be informed of the CEA rise so that the patient could be urgently screened to exclude widespread metastatic disease or a non-malignant cause for the CEA rise. If neither was found, and the patient was medically fit for operation, second-look surgery to locate and remove any treatable recurrence was mandatory. In the case of patients in the 'Conventional' arm, the clinician would not be informed of the 'significant' CEA rise nor of subsequent randomisation to not have the CEA rise revealed.

The primary outcome was survival based on death certification through the Office of Population Censuses and Surveys (OPCS) (now called the Office for National Statistics (ONS)). No subset analyses were planned.

The intention as stated in the protocol was that the trial would produce:

a) a definitive answer concerning the effectiveness of CEA-prompted second-look surgery to improve survival
b) an accurate picture of the 'lead time' produced by CEA compared to clinically indicated second-look surgery
c) further data relating CEA levels to tumour histology and topography, and
d) a large data base on the natural history of colorectal cancer.(4)

The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements give no indication as to the precise nature of analyses that might follow and are regarded as opportunities for explanatory subset analyses which were not in the event carried out.

Methods: the conduct of the trial 1982 to 1993

The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical Trials Centre at King's College Hospital. CEA assays were performed using a radioimmunoassay technique at a single centre at Charing Cross Hospital.

Selection of patients

All patients up to the age of 76 who had undergone a potentially curative resection for adenocarcinoma of the colon or rectum and who were fit and willing to adhere to the post-operative monitoring routine were eligible for the study. Patients were excluded if there was evidence of incurable distant spread, either pre-operatively or during the primary operation, or if the CEA level failed to return to the normal range (<10 ng/ml) within six weeks of primary surgery. Patients who had previously received treatment for other types of cancer, apart from basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix adequately cone biopsied, were excluded from the study.

Management of the primary tumour

A pre-operative blood sample for CEA assay was taken from all patients with suspected colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. This was a pragmatically designed study so each surgeon was at liberty to use their normal operative technique and to employ peri-, or post-operative radiotherapy, or adjuvant chemotherapy as was seen fit, however they were asked to remain consistent regarding the treatment used for any particular type of disease. If at laparotomy, a potentially curative resection was performed and subsequent histology confirmed the diagnosis of adenocarcinoma, the patient was given a full explanation of the study and could be registered.

Baseline data

Following informed consent, the surgeon carried out investigations to detect the presence of synchronous colorectal tumours (both benign and malignant) and to exclude occult liver spread; (usually barium enema examination and ultrasound or CT scan of the liver). In addition, factors that could give raised CEA levels in the absence of recurrent colorectal cancer, such as chronic lung disease, cirrhosis, chronic pancreatitis, and chronic renal failurewere excluded by clinical questioning, chest x-ray, liver function tests, blood urea and electrolytes. Smoking habits and alcohol consumption were also recorded as heavy smoking or drinking, or a change in these habits, can influence CEA levels.

Patient Entry

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Figure 3: Trial flow diagram

Monitoring of Patients

Clinical follow-up of all patients continued in an identical manner (three monthly for the first two years and six monthly for the next three years) whilst blood for CEA assay was drawn monthly for the first three years and three monthly for the next two years. If the patient remained well and the CEA was within normal limits as defined by a pre-tested algorithm, monitoring continued according to the schedule.

CEA assay

Ten mls of whole blood were taken from each patient. The serum was separated and sent to the Trials Centre in special plastic phials. After logging receipt, the samples were forwarded to the Medical Oncology Department at Charing Cross Hospital for assay. The results were returned to the Trials Centre for recording and action if appropriate. This centralised system ensured that all participating clinicians were kept blind to the CEA results for their patients. It also ensured quality control of the CEA assay as there was no possibility of inter-laboratory variation.

Serum CEA values were measured by double antibody radioimmunoassay.(31-33) A bank of serum samples has been retained at -20°C.

Monitoring assay compliance pre-randomisation

Throughout the trial, compliance with blood sampling was monitored by the secretariat. Clinicians were reminded each month of the patients for whom samples were due; those who had missed the previous visit were highlighted as urgent. The percentage compliance for each participating patient was calculated as the number of samples received divided by those expected x 100. The median time between samples was also calculated. Failure to achieve 50% or less of the expected samples was defined as poor compliance. Since the sensitivity to detect CEA rises in such patients was greatly reduced and they were excluded from randomisation.

'Significant' Rises in CEA

A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on two successive occasions and one of the following conditions was also met: the CEA level was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the highest value was more than 7ng/ml above the lowest value ever recorded.
If a 'significant' rise in CEA occurred, the record of the patient was reviewed at the Trials Centre and provided no evidence of suspected colorectal or other disease was recorded in the CRF, the patient was randomised either into an 'Aggressive' or 'Conventional' arm.

Figure 4: CEA algorithm

Randomisation

Patients were randomised equally between the two arms (1:1). Patients whose compliance was between 50 and 70% or whose immediate post-operative sample had not been received within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was also stratified by participating clinician. A block size of two was used in order to maintain as close a balance as possible between the two treatment arms. .

If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise immediately by telephone from the trial centre and subsequently in writing and was requested to contact the patient urgently. Patients were informed of their situation including the fact that they had been randomised within the trial to undergo a second-look procedure. This was then undertaken if the patient gave informed consent. The surgeoncarried out a full clinical work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g., change in smoking or drinking habit) and to identifyany incurable distant spread. In the absence of these conditions the surgeon undertook a mini-laparotomy, proceeding tofull laparotomy with macroscopic clearance of disease, should this be possible.

For patients randomised to the 'Conventional' arm no further action was taken; the clinician was not informed that the CEA had risen nor that the patient had been randomised.

If at any stage a patient in the study developed clinical evidence of recurrent disease the clinician was at liberty to manage the patient according to usual practice. If the disease was in the abdomen and was thought to be treatable by a second-look operation with re-resection, this was perfectly acceptable. The clinician was blind as to whether such patients had been randomised to the 'Conventional' arm of the trial or had not been randomised because the CEA had failed to denote the presence of recurrent disease.

Second-Look Laparotomy

The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was detected all that was required prior to closure, was biopsy. Otherwise following a full excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis was undertaken. The liver was fully mobilised to determine whether any tumour was present. Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then carried out with the objective of total extirpation of all recurrence. Complete data recording of the procedure along with the results of the histology of all potentially involved sites was required by the trial's office.

For patients in whom a radical resection was achieved after second-look surgery (motivated either on clinical information or because the patient had been randomised to the 'Aggressive' arm) the follow-up schedules for clinical examination and blood sampling reverted to those following the primary operation. However, for patients randomised to the 'Aggressive' arm, clinicians were immediately notified of any further CEA levels above 10ng/ml.

Death

Every patient registered onto the study was 'flagged' with the Office of Population Censuses and Surveys (OPCS) who provide automatic notification of date of death. This enabled the trial centre to receive certified cause of death for all patients.

Trial oversight

A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not entering patients into the trial was asked to review the data after the first 100 patients had been randomised, which occurred in January 1988, and again after 200 patients had been randomised in February 1993, at which point it was recommended that the trial was stopped since it was very unlikely that any clinically important advantage would be demonstrated for patients undergoing second-look surgery.

Methods of the RIAT process

The data

The RIAT restorative authors had been warned by the statisticians called in to look at the data in 2003-4 that “the databases were corrupted with key variables no longer abstractable” and that they could not be analysed without a lot of work.(34;35) We found that the data on paper and on file were accessible and we had no reason to doubt the veracity of individual items. We found that the electronic files had numerous problems with formatting which

made the files on the 1447 individual patients difficult to handle but that the data entries were not themselves corrupted.

One of the RIAT restorative authors (KM) had worked in the trials units during the time the CEA Trial data were being accrued and knew the systems in use and their changes but was not directly involved in this trial at any stage.

The questions raised and the problems encountered, were resolved as follows:

- The codes indicating that a patient had met the criteria for CEA elevation and whether they were randomised to 'active' or 'Conventional' arm were preserved and tallied with the number in the 1994 manuscript.(30)

- There were variations in the way dates were recorded in the database. There had been migrations of data from a 'Prime' server using 'Universe' to 'Excel' and the interpretation of the present authors, with information from contemporary witnesses was that in undertaking the task operators did not always correctly specify these data as 'dates' when importing, and/or allowed them to be converted to American date formats. These errors prevented calculations and would have defeated running a survival analysis without correction of the file entries. The dates were however visually readable and not 'corrupt'. Some could be corrected by running current versions of software. Others were manually corrected by re-entering them in a Microsoft date format. Paper records were available to resolve uncertainties.

- The next problem was in linking these three groups of patients (randomised to 'aggressive', randomised to 'conventional' and not randomised) to the dates for survival analysis. Individual patients were uniquely identified in the files by seven digit strings to which letters had been added at the beginning and end, possibly for trial administrators' checklists or subgroup identification. Oncewe had established that the initial and terminal letters were redundant for analysis of the primary endpoint, we were able to write code to restore the seven digit strings.

- It was evident that the seven digits did not represent a simple sequence but certain positions identified particular characteristics, such as participating centre. We recognised a consistent pattern of mismatch in the fourth digit, a zero in one file was an 8 in the other with all other digits remaining the same. It was suggested to us that the fourth digit replacement was used to identify patients suitable for *post hoc* subgroup analyses but no documentation was found to confirm this. By checking back to the dates of birth we were able to confirm that this systematic correction resolved the problem and most of the data were then usable.

- By ranking all the data in the paired files for line by line visual inspection residual discrepancies were identified. Scrutinising the digit strings allowed for seven of the remaining eight pairs to be reconciled and verified on dates of birth. We failed to resolve only one out of 1447 records in each file. This patient had not been randomised.

- Inspection of the accrual of death dates was discontinuous for a couple of years suggesting a lapse in either recovery or entry. The current trials centre obtained permission to re-run the Office for National Statistics (ONS) search in July 2012.

In summary, we identified several problems but they were systematic and not random (we would not use the value laden word 'corrupted'). We were able to rectify the formatting errors and verify that the data used for our analysis were correct. The Kaplan Meier analysis was re-run.

Results

The original main results 1994

The study opened to recruitment in November 1982 and was closed by the Working Party, on the acceptance of a recommendation from the Data Monitoring Sub-committee, on 17th February 1993. During this period 1,447 patients were registered by 73 participating clinicians in 58 hospitals in the United Kingdom and Europe. Of these 39 (2.7%) were deemed ineligible since their CEA did not fall below 10 ng/ml by six weeks after surgery. A further 173 patients were excluded from analysis; four did not have a confirmed diagnosis of adenocarcinoma, 6 were considered unfit for continued monitoring, 4 had a previous and 1 a simultaneous non-colorectal malignancy, 2 had metastatic disease, and 156 (10.8%) never complied with the requirement for monthly blood sampling or only did so for 3 months or less.

Figure 5

Of 1,235 patients who continued in the trial, 80% achieved a greater than 60% compliance with blood sampling, whilst 12.5% registered between 40-59% of the required samples and only 7.5% had compliance of less than 40% The majority of randomisations (160/216; 74%) were prior to the second anniversary of the primary diagnosis. Three patients randomised had prior recurrent (2) or metachronous (1) disease detected clinically, without a rise in CEA and were operated upon.

Two hundred and sixteen patients developed a 'significant' rise in CEA and as no recurrent disease had been recorded at their latest trial follow-up, they were randomised by the Trial Office (108 to each arm). The median time from primary surgery to randomisation was 403 days, (range 103 to 1754) with no statistical difference between the two groups.(30)
The characteristics of patients in the two groups are given in Table 1.

Table 1

	Aggressive N=108	Conventional N=108
Sex male (%)	60(56%)	68(63%)
Age years, median and range	64 (33-75)	62 (35-75)
Pathological stage	N(%)	N(%)
Dukes' A	5 (4.6)	5 (4.6)
Dukes' B	46 (42.6)	49 (45.4)
Dukes' C[1]	36 (33.3)	38 (35.2)
Dukes' C[2]	17 (15.7)	10 (9.3)
Missing	4 (3.7)	6 (5.6)

The stage mix of 980 patients who were eligible for inclusion in the randomised trial but who did not have a CEA rise as defined was Dukes' A 15.1%, B 55.2%, C1 23.3%, C2 6.4%.

Of the patients randomised to the 'Aggressive' arm 83 (77%) had recurrent cancer identified and 62 (57%) patients had 'second-look' surgery. In patients randomised to the 'Conventional' arm 89 (82%) had developed recurrent disease by the date of analysis. In these 26 (24%) second-look procedures were undertaken. By February 1993, 91/108 in the the 'Aggressive arm' had died and 88/108 patients had died in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37).(30) It was considered by the data monitoring committee to be "highly unlikely that any survival advantage would be demonstrated for patients undergoing second-look surgery". This was communicated to the trial centre.

RIAT restoration and updated survival analysis

The data were restored by the RIAT authors for 1446 of 1447 patients to the extent that the RIAT authors were confident of their dates of birth, death and whether they met criteria for entry into the controlled trial and then to which arm they were allocated.

The electronic records were intact with respect to the identity of the patients, which patients had reached the criteria for randomisation, and the trial arm to which they had been randomly allocated for all 216 patients who were randomised. The sex, age, primary site and Dukes' stage as recorded in the 1994 manuscript are shown in Table 1.

Certification of death was obtained from ONS on behalf of the RIAT restorative authors for 204 of 216 randomised patients who died between 17/10/1983 and 08/09/2011. There were equal numbers of patients in the two arms (108) and equal numbers of death dates were retrieved (102). We also have dates of death in 862 of the 1230 patients who were not randomised. Kaplan Meier analysis in these three groups is shown in Figure 6, showing survival of the 1230 participants who entered the trial but were not randomised the 108 participants in each arm randomised to have the CEA disclosed or not disclosed to the surgeon.

Figure 6 Kaplan Meier analysis

The lead time conferred by CEA monitoring, defined as the median time to clinically detected disease for patients randomised to the 'Conventional' arm, was 323 days (SE 60; 95% confidence interval (CI) 203-443). This analysis included censored observations on 23 patients, however only five of these had a censored time less than the lead time. It was regarded as unlikely, therefore, that the lead time would decrease as further events occur. The analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs 70% at a year. The RIAT authors did not repeat this analysis.

Discussion

We have restored data sufficient to achieve the primary outcome of interest as specified by the CEA trialists:

> "Does a policy of CEA-prompted second-look surgery following 'curative' resection of colorectal cancer produce a decrease in morbidity and mortality due to tumour recurrence, despite sequelae of second look surgery?"

The answer is that acting on CEA elevation by second-look surgery did not reduce mortality compared with patients in whom similar CEA elevation remained unknown. This negative finding led to the closing of the trial in 1994(21;22) and we confirm it here. There was small non-significant excess of deaths in the 'Aggressive' arm. The burden of morbidity attributable to the greater number of investigations and operations was not captured by the trial protocol.

The second planned analysis was to obtain an accurate picture of the 'lead time' produced by CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up patients considerably sooner than the clinical methods available at the time by about six months to a year.

CEAmonitoring is currently used by some for this purpose but in development of the PulMiCC trial we found variability in its use and inconsistency in the threshold used.(29) Other methods of investigation (MRI, PET and improved CT and echo) are now used to detect recurrence before it is clinically evident. It cannot be presumed, and on the basis of the CEA Second-Look Trial results there is doubt, that earlier detection by these newer methods, leading to further surgery, leads to better outcomes.

The third and fourth intentions set out by the CEA trialists were c) to obtain further data relating CEA levels to tumour histology and topography and d) a large data base on the natural history of colorectal cancer. Multiple CEA assay results exist in the data we hold for 1446 patients and it would be possible to link these to survival as a result of the RIAT restorative work..

With respect to the natural history of colorectal cancer although we trust the death certification data for the date of death it has been shown that "at least a third of all death certificates are likely to be incorrect"(36). No doubt aware of this and seeking much more detailed information, the CEA Trialists had asked for detailed post-mortem examinations. Given the many differences in cancer evaluation and imaging in the intervening thirty years we would be cautious about their value now.

It appears that it was disagreement concerning explanatory analyses which contributed to the failure to publish the primary outcome of interest.(30) The purpose of such analyses is to discover subsets of patients in whom there was a benefit from the intervention under evaluation and to thus determine the characteristics of patients in whom the intervention might have had a beneficial effect by analysis of mediators and moderators.(37) There is a general objection to this exercise because it can lead to spurious associations.(38;39) Furthermore when there is no overall benefit found, as in the CEA Second-Look Trial, any subgroup(s) where there is a positive association between intervention and outcome must be balanced by one or more other groups where there was net harm. There were no completed subset analyses in 1994 and we have not attempted any in restoring the trial.

The answer to the primary research question was clear in 1993 and was the explicit reason for stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery had been missed and in the absence of benefit there was net harm being done to the patients. We cannot say whether this is inevitability associated with any form of second-look surgery for colorectal cancer or whether these findings will apply to any other means of selecting

patients for second-look surgery. The forms of second look surgery now widely practiced in colorectal cancer are liver and lung resection of metastases.

- Full mobilisation of the liver at second-look laparotomy was included in the CEA Trial protocol. Hepatic resection has entered routine practice based on observational data(40) and an opportunity to do a randomised trial, for which a power calculation was proposed in 1992 from the Mayo Clinic(41) was not taken.(23)
- Two patients had a thoracotomy prompted by CEA elevation. Pulmonary metastasectomy for colorectal cancer is, after primary lung cancer, the second commonest thoracic cancer operation and is the subject of an ongoing randomised controlled trial.(42)

If the CEA Trial findings can be generalised, and there is no obvious reason in principle why they should not be, it would suggest that more critical scrutinyof the evidence base that was used to bring surgery for advanced colorectal cancer, and specifically liver and lung metastasectomy into practiceis warranted.(23;28) The CEA Trial was a well-conceived and meticulously executed randomised trial and we hope that publishing it now more than twenty years after its completion will indicate the possibility of more randomised trials in surgery.(43)

Legends

Figure 1. The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.(4)

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.(12)

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.(4)

Figure 4. Decision making algorithm for CEA to trigger second-look surgery.(12)

Figure 5. Flow chart of enrolled and ultimately randomised patients. 'Blind' in the bottom left box means that the clinical teams were unaware of the elevated CEA discovered and were unaware that the patients have been randomised. They were indistinguishable amongst the 1230 non-randomised patients who were being followed-up. (See Figure 6)

Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from Office for National Statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230) Some would have had clinically evident early recurrence precluding randomisation. The initial plateau is an illustration of a death free interval(44) or "immortal time bias"(45) Patients in prospective studies may have a built in obligatory survival time from some starting point in order to attain the requirements to be included in the data set. This is an artefact but may be absorbed into survival time adding to and not readily distinguished from survival time attributed to treatment.

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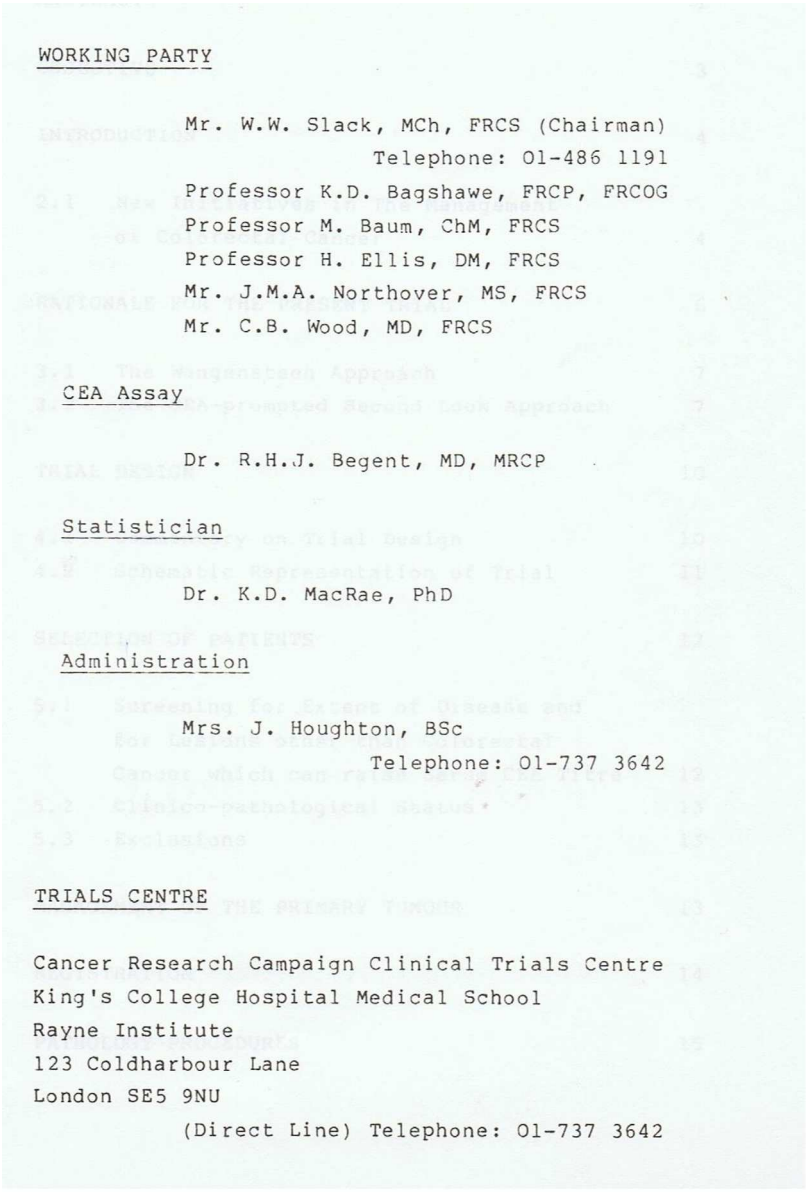

WORKING PARTY

Mr. W.W. Slack, MCh, FRCS (Chairman)
Telephone: 01-486 1191
Professor K.D. Bagshawe, FRCP, FRCOG
Professor M. Baum, ChM, FRCS
Professor H. Ellis, DM, FRCS
Mr. J.M.A. Northover, MS, FRCS
Mr. C.B. Wood, MD, FRCS

CEA Assay

Dr. R.H.J. Begent, MD, MRCP

Statistician

Dr. K.D. MacRae, PhD

Administration

Mrs. J. Houghton, BSc
Telephone: 01-737 3642

TRIALS CENTRE

Cancer Research Campaign Clinical Trials Centre
King's College Hospital Medical School
Rayne Institute
123 Coldharbour Lane
London SE5 9NU
(Direct Line) Telephone: 01-737 3642

The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.(4)
152x227mm (200 x 200 DPI)

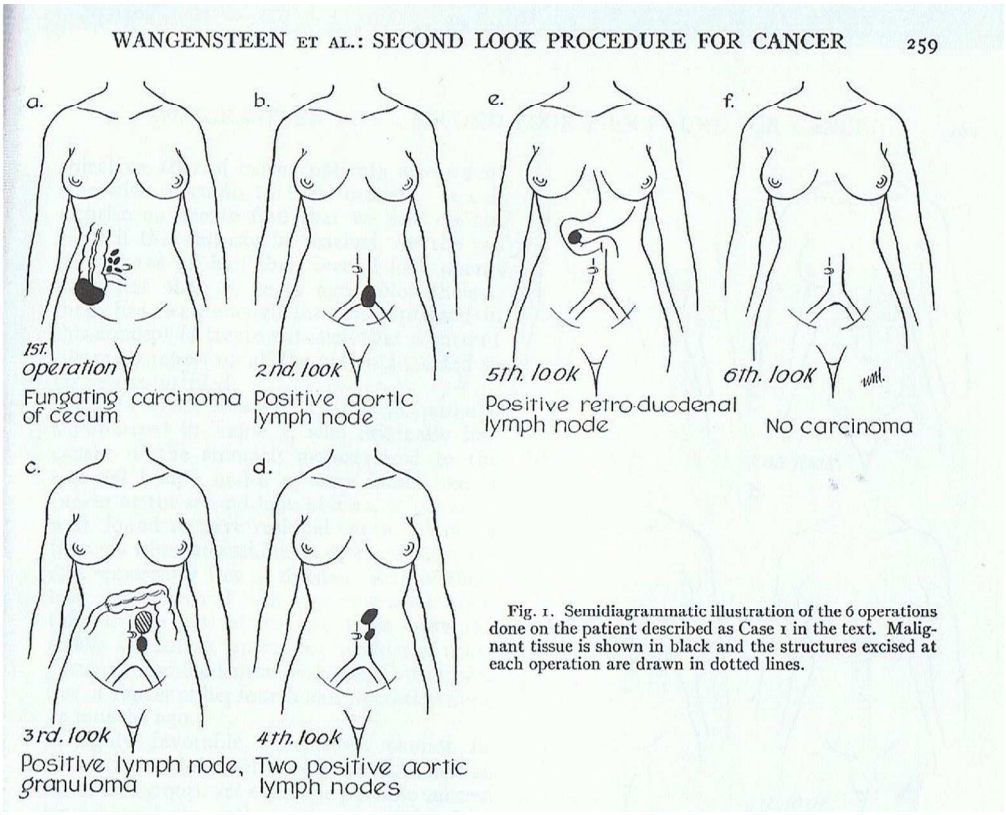

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]
111x90mm (300 x 300 DPI)

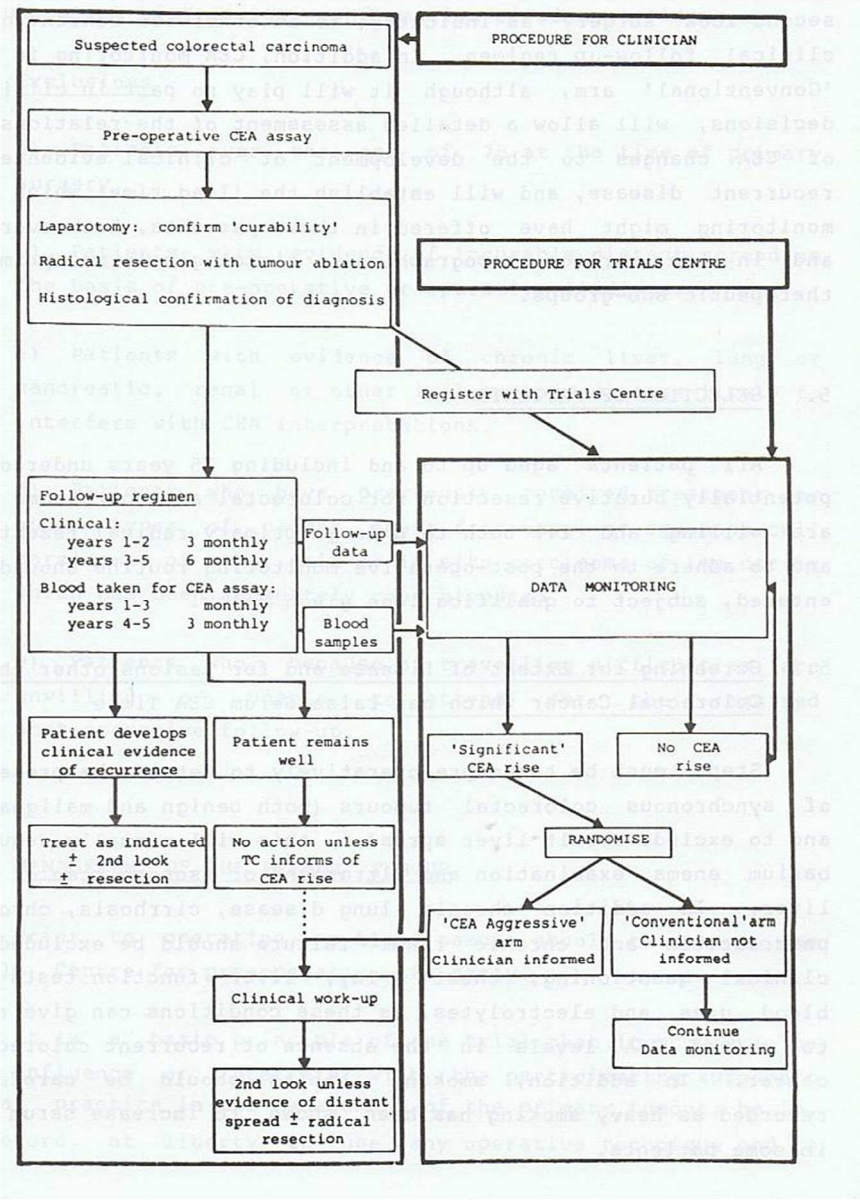

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]
64x90mm (300 x 300 DPI)

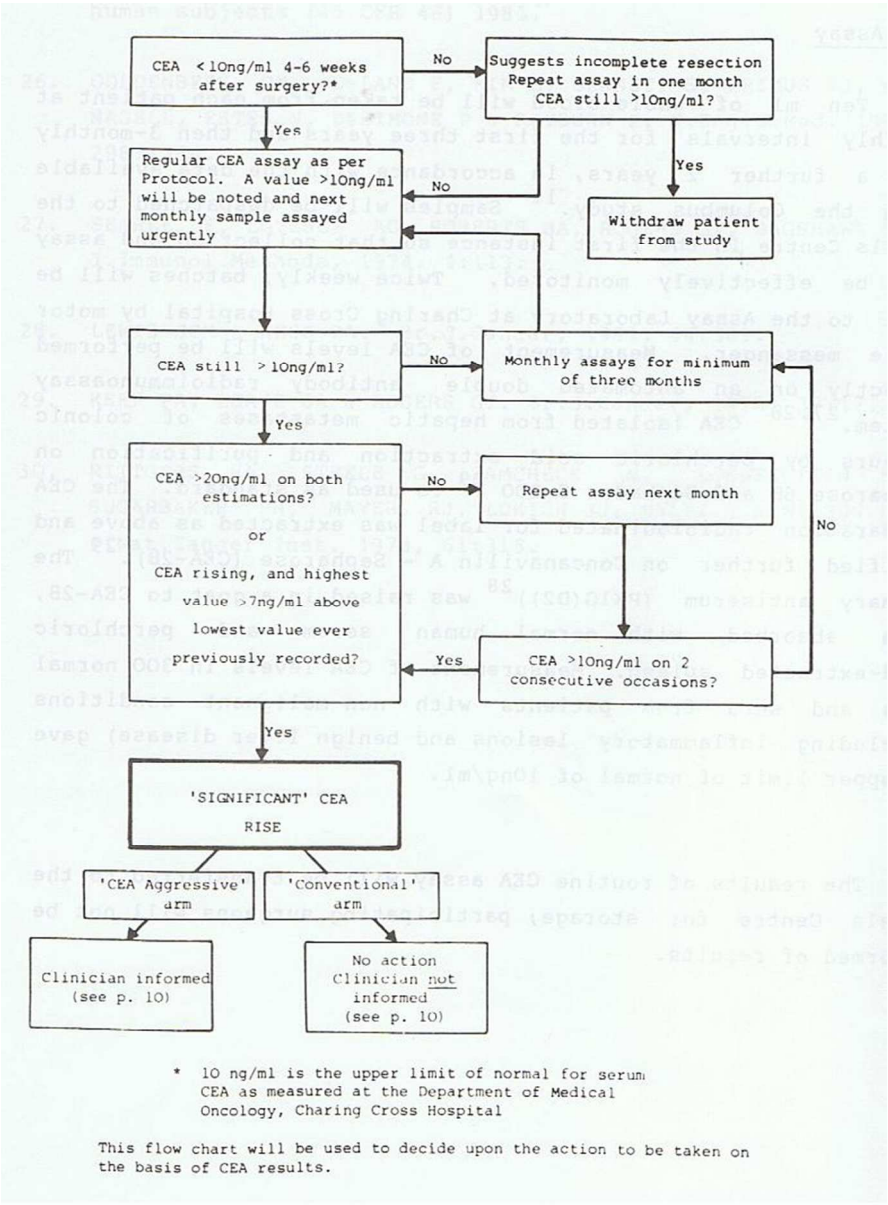

Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22]
66x90mm (300 x 300 DPI)

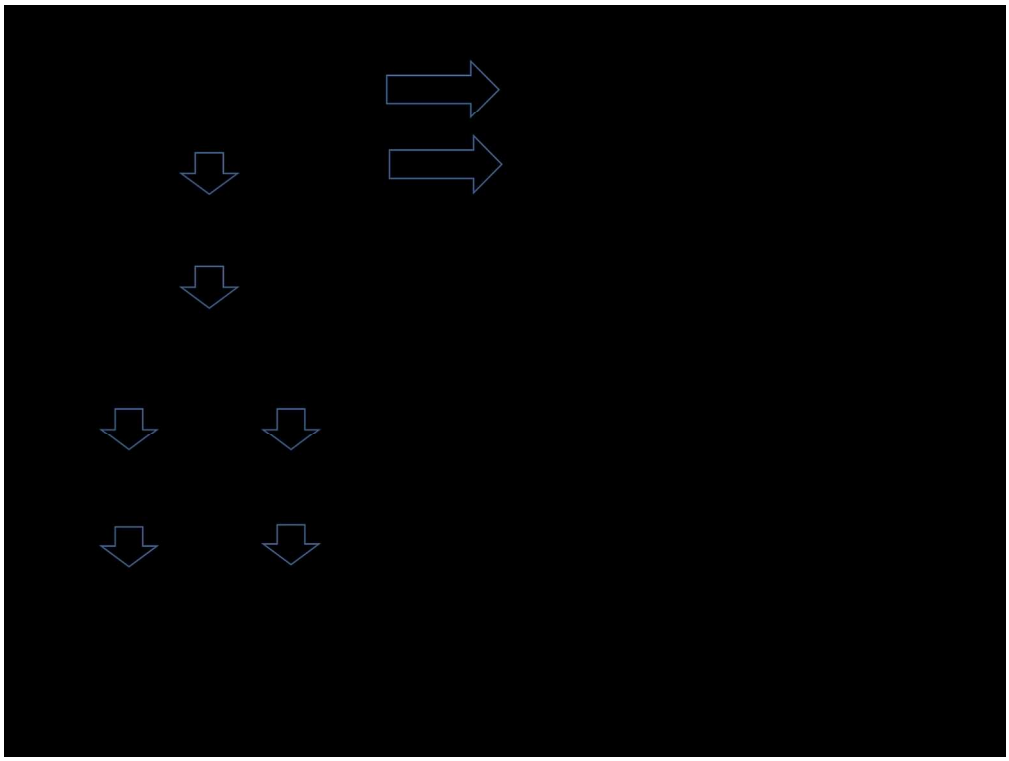

Figure 5. Flow chart of enrolled and ultimately randomised patients
119x90mm (300 x 300 DPI)

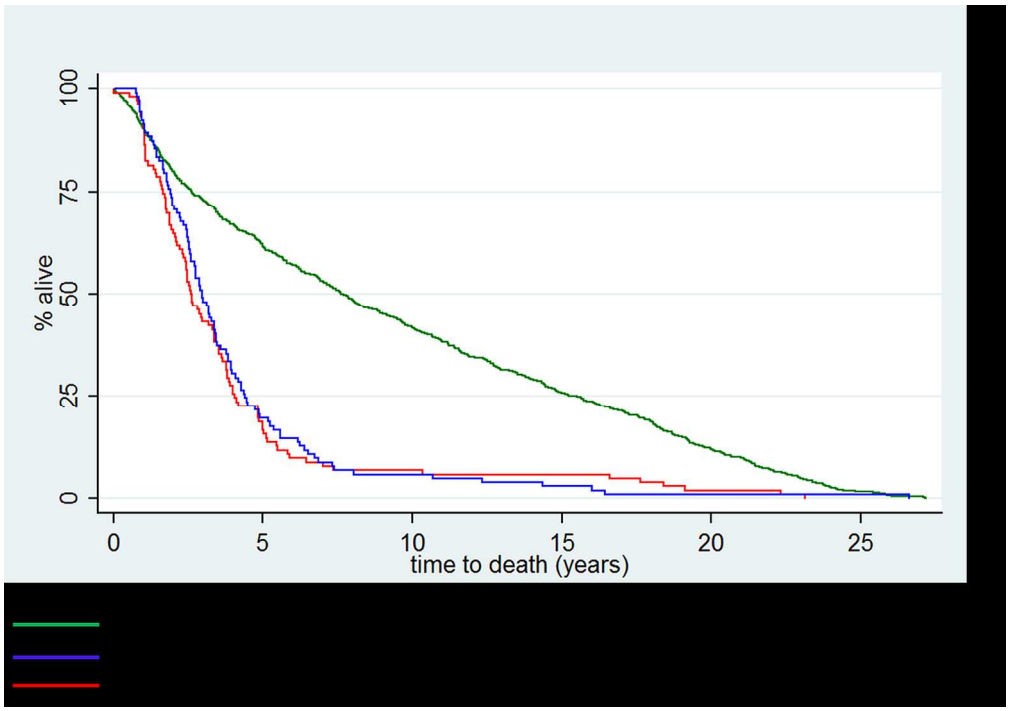

Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from ONS statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230) Some would have had clinically evident early recurrence precluding randomisation. The initial plateau is an illustration of a death free interval[44] or "immortal time bias"[45] Patients in prospective studies may have a built in obligatory survival time from some starting point in order to attain the requirements to be included in the data set. This is an artefact but may be absorbed into survival time adding to and not readily distinguished from survival time attributed to treatment.

RIAT Audit Record (RIATAR)

*A tool for documenting the transformation from regulatory documents to journal publication, based on the CONSORT 2010 checklist of information to include when reporting a randomised trial**

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
Title and abstract						
	1a	Identification as a randomised trial in the title	1	Cover	1	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3	1-2	None written	
Introduction						
Background and objectives	2a	Scientific background and explanation of rationale	5-6	4-9	None written	
	2b	Specific objectives or hypotheses	3	2	2	
Methods						
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	10-11	2	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	None	None	None	
Participants	4a	Eligibility criteria for participants	7-8	12-13	2-3	
	4b	Settings and locations where the data were collected	12	Not stated	Not stated CEA assays 4	This was of course implicit that these were in units performing colorectal cancer

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
						surgery within hospitals
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10	16,18	4, 6-7	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed. NOTE “lead time” was a planned analysis There was also reference to “parallel studies”	7	2 21	7	I cannot see that this was explicitly stated in current terminology but it was all cause mortality and that is implicit throughout and not in doubt.
	6b	Any changes to trial outcomes after the trial commenced, with reasons	None	None	None	
Sample size	7a	How sample size was determined	10-11	19	7	Lacks clarity and 2000 suggests a degree of “ballpark” but it is there.
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10-11	19	7-8	
Randomisation:						
Sequence generation	8a	Method used to generate the random allocation sequence	9		5	
	8b	Type of randomisation; details of any	9		5	This is not very

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
		restriction (such as blocking and block size)				detailed but is all we found.
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9-10		5-6	This was dealt with in some detail in the 1994 manuscript.
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10			Patients were enrolled by participating clinicians and it is quite clear that it was the trial centre that randomised.
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	10			
	11b	If relevant, description of the similarity of interventions				
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13			
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A			
Results						
Participant flow	13a	For each group, the numbers of	12-13		9	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
(a diagram is strongly recommended)		participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome				
	13b	For each group, losses and exclusions after randomisation, together with reasons	13 Lines 506-10 are the restorative analysis		None recorded	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12		9	
	14b	Why the trial ended or was stopped	12		9	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13		17	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12 12 13		11	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Survival 13 Lead time 14		10 9	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended				
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory				

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not dealt with			I don't think the data are good enough to document these and they are implicit in the stopping decision. They could be discussed if required.
Discussion						
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14			
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15			
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15			
Other information						
Registration	23	Registration number and name of trial registry				
Protocol	24	Where the full trial protocol can be accessed, if available	UCL			
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	None		CRC	

* The aim of this audit tool is provide a permanent record of the parts of text, tables and figures of the source Clinical Study Report (CSR) selected for inclusion into the RIAT manuscript submitted for publication. This tool is based upon checklist items described in the CONSORT 2010 statement, which is a widely adopted standard for reporting randomised trials. RIAT authors should consult the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. Similar audit records can be created for other types of trials by adapting other CONSORT extensions, e.g. for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. See www.consort-statement.org for more details.

BMJ Open

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Colorectal surgery < SURGERY, Chemical pathology < PATHOLOGY, Adult oncology < ONCOLOGY, Adult gastroenterology < GASTROENTEROLOGY, CHEMICAL PATHOLOGY

Title

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

Tom Treasure[1]
Kathryn Monson[2]
Francesca Fiorentino[3]
Christopher Russell[4]

[1]Clinical Operational Research Unit, University College London

[2] Sussex Health Outcomes Research & Education in Cancer (SHORE-C)
Brighton & Sussex Medical School, University of Sussex, Falmer, Brighton

[3] Department of Cardiothoracic Surgery, NHLI, Imperial College London

[4] Surgery, University College London, London

Abstract

Objectives: in patients who have undergone a potentially curative resection of colorectal cancer does a 'second-look' operation to resect recurrence, prompted by monthly monitoring of carcinoembryonic antigen, confer a survival benefit?

Design: a randomised controlled trial recruiting 1982 to 1994 recovered under the RIAT initiative (Restoring Invisible and Abandoned Trials).

Setting: 58 hospitals in the United Kingdom.

Participants: from 1982 to 1993, 1447 patients were enrolled. Of these 216 met the criteria for CEA elevation and were randomised to 'Aggressive' or 'Conventional' arms.

Interventions: 'second-look' surgery with intention to remove any recurrence discovered.

Primary outcome measure: survival.

Results: by February 1993, 91/108 patients had died in the 'Aggressive arm' and 88/108 in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37). By 2011 a further 25 randomised patients had died. Kaplan Meier analysis showed no difference in long-term survival.

Conclusions: the trial was closed in 1993 following a recommendation from the Data Monitoring Committee that it was highly unlikely that any survival advantage would be demonstrated for CEA prompted second-look surgery. This conclusion was confirmed by repeat analysis of survival times after twenty years.

International Standard Randomised Controlled Trial Number ISRCTN76694943

Date applied 1st July 2001 and recorded as 'completed'

Strengths and limitations of this study

- The CEA Second-Look Trial was a well-planned and carefully executed study with a clear question and a well-defined outcome of interest.
- Second-look surgery prompted by the best available indicator of recurrence at the time conferred no survival advantage.
- A further strength, and a reason to publish this trial now, is that it shows that randomised trials in surgery can be done and that the result may be contrary to the beliefs and expectations of practitioners based on their uncontrolled observations.

A limitation is that present day means of non-invasive detection of asymptomatic recurrence were not available at the time of the CEA Second-Look Trial. A recently reported randomised controlled trial (FACS) in which regular CEA and/or CT monitoring were compared with minimum follow-up showed no survival advantage associated with earlier detection through monitoring.

Introduction

The Working Party of the Carcinoembryonic antigen (CEA) Second-Look Trial set the scene for their trial in their protocol in 1982(1) The principle finding, that CEA monitoring to detect asymptomatic recurrence was not associated with improved survival, was announced in a letter to the Journal of the American Medical Association in 1994 by Northover, the then Chief Investigator.(2) The writing of the trial for publication lapsed. We here report the trial under the RIAT initiative (Restoring invisible and abandoned trials).(3;4)

It had been observed during the 1970s that the outlook for patients with colorectal cancer was not good. Only one in four patients survived for five years after diagnosis and radical surgery was observed to be curative in under half of patients (5). Results had not improved in several decades.(1;6;7). Refinements in primary operative techniques had not made a difference(8) and it was considered unlikely that technical modifications would lead to improvement in survival following surgery.(5;6) Routine surgical follow-up had not led to further surgery being shown to be beneficial: clinical evidence of recurrence usually meant that the tumour would be unresectable at second-look laparotomy.(9) The published experience of members of the Working Party who developed and launched the trial was that of 180 patients, followed up from six months to 15 years, with a total of 2319 out-patient clinic visits, only one patient could be considered to have had a potentially curative second-look operation.(10) They concluded that to re-resect with prospect of benefit, recurrence had to be detected before it was clinically evident(1) but more pro-active clinical follow-up of asymptomatic patients by three monthly sigmoidoscopy, barium enema and chest X-ray (the methods available at the time) had failed to show improvement in 5-year survival.(11) Nevertheless, there had been several reports of 30% five-year survival in selected patients after radical resection of recurrent cancer(7;12;13) and resection was believed to sometimes lead to "cure".(7;12-14)

Improving detection and treatment of recurrent disease: the context in1982

The trial development group considered the evidence available at the time for methods of detecting recurrence early and a founding principle of the CEA Second-Look Trial was that early detection of recurrent tumour would only be justifiable if further treatment offered the prospect of benefit to the individual patient.(1) The evidence available to the trial working party in 1982 is outlined below.

Figure 1 Working Party membership

The Wangensteen Approach:

During the 1950s the systematic use of a policy-based second operation was reported. Patients at high risk of recurrence (those with Dukes' Stage C tumours) were re-operated on at 6-monthly intervals, resecting recurrence when found, until they were 'tumour free'. If cancer had been found the patients were scheduled for 3rd and more "looks", up to six further abdominal operations, "before the abdomen was free of cancer". Once a patient had undergone a negative laparotomy, no more surgery was recommended. Sixty-four patients with colon or rectal cancer were managed in this way. In 35 (55%) of them the "second-look" laparotomy was negative for the discovery of recurrent cancer, seven of whom subsequently had clinical recurrence. There were four (6%) operative deaths.(15) The Working Party concluded that this 'blanket second-look' policy might have produced some

"cures" but entailed high rates of negative laparotomy and an unacceptable operative mortality rate.(1)

Figure 2 from Wangensteen 1954

The CEA-prompted Second-Look Approach

CEA had been shown to detect recurrence of colorectal cancer following surgery.(16-21) CEA rose, on average, four months prior to clinical evidence of recurrence(17) and there were reports of the use of serial serum carcinoembryonic antigen (CEA) assays to detect asymptomatic recurrences in the belief that curative resection would be possible more frequently.(16-18) Several groups used CEA in this way, and found low false positive rates(9;22) and the resectability rate of the recurrence was higher than when clinical criteria were used to prompt re-operation.(9) In the largest published experience of CEA in a post-operative monitoring role(9;16) recurrent tumour, which was resectable, was found in 70% in whom re-operation was prompted by a rise in the serum CEA compared with a quarter of patients undergoing second-look laparotomy prompted by clinical indications. Others had not found CEA to be useful in this post-operative monitoring role. Even if efficacy of CEA detected recurrence was accepted, there was still the unresolved question of effectiveness: if more patients were detected and there were more instances of resectable recurrence, did that lead to better survival and patient benefit? The conflicting interpretations of observational data resulted in calls for trials(16;22;23) including one within a 1981 NIH Consensus Statement.(21)

The objective of the CEA Second-Look Surgery Trial was to determine whether, following potentially curative primary surgery for colorectal cancer, mortality could be decreased by a policy of second-look surgery prompted by rising serum carcinoembryonic antigen (CEA). The trial ran from 1982 to 1993. The main result, that there was no survival advantage, was reported in 1994 to the British Oncological Association(24) and was published in a letter to the Journal of the American Medical Association.(2)

Detection and reoperation for asymptomatic colorectal cancer recurrence has since become routine both in the form of hepatic resection(25) and pulmonary metastasectomy(26) but without evidence from controlled trials for either practice.(27;28) When doubts were raised about the security of the evidence in the British Medical Journal in 2007(27) a general belief existed that randomised controlled trials of the effectiveness of resection of liver or lung metastases were not possible and were not needed. These paired beliefs are brought into question by the previously unpublished CEA Second-Look Trial: a randomised trial had been done and the presumed benefit of surgery for cancer recurrence was not seen.(2;24)

Closure of the trial in 1993 and gaining access to the data in 2011

The RIAT restorative authors had been involved in various studies related to surgery for disseminated colorectal cancer(27;29;30) including a conundrum as to whether discovery of an elevated CEA assay should prompt, or be considered a contra-indication to, pulmonary metastasectomy.(31) We knew the CEA trial had been recruiting in the 1980s but when we searched the literature for the result of the trial found nothing later than 1994.(2;24) In 2009 we contacted the chief investigator of the trial at the time of its closure (JMAN) and the present director of the University College London Cancer Trials Centre (JAL). We were

informed that the data were irretrievably lost. However, staff at UCL CTC were aware that CEA trial data were still in the department and after further enquiries RCGR gained access to anonymised electronic data in 2011. The process of data restoration is described later. It was agreed that the trial would be published as part of 'Restoring invisible and abandoned trials'(RIAT).(3;4)

Amongst the documents made available to the RIAT restorative authors were listed the members of the trial development group in the 1982 protocol(1) and the contributors to the 1994 manuscript.(32) None of these individuals expressed an interest in resuming work on the trial or were in a position to do so. When we contacted them later to share the restored data with them no one raised any objection but on the contrary encouraged us to publish their findings.

Methods: trial intent and design

The recruitment intentions and the trial protocol as presented here are essentially as written in the manuscript prepared in 1994 with the full intention of publishing the trial.(32) The text has been edited by the RIAT authors but no new material has been introduced.

The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years and to follow them for five years. The study was specifically designed with late randomisation in order to maximise statistical power. It was originally intended to recruit 2,000 patients with the anticipation that about 25% would show a CEA rise as the first evidence of possible recurrence. This number would have provided 95% power to detect an improvement in two year survival from the second-look procedure from 25% to 55% at α=0.05. The protocol stated that for the trial to be stopped prematurely very stringent levels of significance ($p<0.001$) would be used. Analyses of the randomised groups were to be by Kaplan-Meier lifetables and the logrank test on 'intention to treat'.(32)

Their intentions were explicitly set out as follows in 1981:(33)

'So far as society in general is concerned, if CEA monitoring is shown to be of benefit in this study, then it will be a powerful incentive to the great majority of surgeons who see no obvious advantage in routine CEA monitoring to adopt the technique; as colorectal cancer is the second commonest killing cancer in the Western world, the benefits would thus be enormous. If, however, CEA monitoring is shown to be of no long term therapeutic value then it should cease to be used in its presently available form, and patients will thereby be spared the 'needless anxiety' of premature knowledge of their impending death.(23)'

The CEA trial design was devised so that clinical follow-up would remain unbiased, and allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent colorectal cancer. After potentially curative surgery for colorectal cancer, all eligible patients were to be monitored identically using conventional clinical follow-up together with regular CEA assay, performed centrally. Clinicians would not be informed of the result. When a 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm, the clinician would immediately be informed of the CEA rise so that the patient could be urgently screened to exclude widespread metastatic disease or a non-malignant cause for the CEA rise. If neither was found, and the patient was medically fit for operation, the protocol

required second-look surgery to locate and remove any treatable recurrence. In the case of patients in the 'Conventional' arm, the clinician would not be informed of the 'significant' CEA rise nor of the fact that they had been randomised to not have the CEA rise revealed.

The primary outcome was survival based on death certification through the Office of Population Censuses and Surveys (OPCS) (now called the Office for National Statistics (ONS)). No subset analyses were planned.

The intention as stated in the protocol was that the trial would produce:

a) a definitive answer concerning the effectiveness of CEA-prompted second-look surgery to improve survival
b) an accurate picture of the 'lead time' produced by CEA compared to clinically indicated second-look surgery
c) further data relating CEA levels to tumour histology and topography, and
d) a large data base on the natural history of colorectal cancer.(1)

The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements give no indication as to the precise nature of analyses that might follow and are regarded as opportunities for explanatory subset analyses which were not in the event carried out.

Methods: the conduct of the trial 1982 to 1993

The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical Trials Centre at King's College Hospital. CEA assays were performed using a radioimmunoassay technique at a single centre at Charing Cross Hospital.

Selection of patients

All patients up to the age of 76 who had undergone a potentially curative resection for adenocarcinoma of the colon or rectum and who were fit and willing to adhere to the post-operative monitoring routine were eligible for the study. Patients were excluded if there was evidence of incurable distant spread, either pre-operatively or during the primary operation, or if the CEA level failed to return to the normal range (<10 ng/ml) within six weeks of primary surgery. Patients who had previously received treatment for other types of cancer, apart from basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix adequately cone biopsied, were excluded from the study.

Management of the primary tumour

A pre-operative blood sample for CEA assay was taken from all patients with suspected colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. This was a pragmatically designed study so surgeons were at liberty to use their normal operative technique and to employ pre- or post-operative radiotherapy or adjuvant chemotherapy as was seen fit, however they were asked to remain consistent regarding the treatment used for any particular type of disease. If at laparotomy, a potentially curative resection was performed and subsequent histology confirmed the diagnosis of adenocarcinoma, the patient was given a full explanation of the study and could be registered.

Consent

The 1982 protocol includes a consent form (Consent form A) to be completed at registration and a further form (Consent form B) for patients who were randomised to a 'Second-Look Laparotomy'. There was a protocol amendment in which the word 'cancer' is to be replaced throughout by 'a growth'.(1)

Baseline data

The surgeon carried out investigations to detect the presence of synchronous colorectal tumours (both benign and malignant) and to exclude occult liver spread; (usually barium enema examination and ultrasound or CT scan of the liver). In addition, factors that could give raised CEA levels in the absence of recurrent colorectal cancer, such as chronic lung disease, cirrhosis, chronic pancreatitis, and chronic renal failure were excluded by clinical questioning, chest x-ray, liver function tests, blood urea and electrolytes. Smoking habits and alcohol consumption were also recorded as heavy smoking or drinking, or a change in these habits, can influence CEA levels.

Figure 3: Trial flow diagram

Monitoring of Patients

Clinical follow-up of all patients continued in an identical manner (three monthly for the first two years and six monthly for the next three years) whilst blood for CEA assay was drawn monthly for the first three years and three monthly for the next two years. If the patient remained well and the CEA was within normal limits as defined by a pre-tested algorithm, monitoring continued according to the schedule.

CEA assay

Ten mls of whole blood were taken from each patient. The serum was separated and sent to the Trials Centre in special plastic phials. After logging receipt, the samples were forwarded to the Medical Oncology Department at Charing Cross Hospital for assay. The results were returned to the Trials Centre for recording and action if appropriate. This centralised system ensured that all participating clinicians were kept blind to the CEA results for their patients. It also ensured quality control of the CEA assay as there was no possibility of inter-laboratory variation.

Serum CEA values were measured by double antibody radioimmunoassay.(34-36) A bank of serum samples has been retained at -20°C.

Monitoring assay compliance pre-randomisation

Throughout the trial, compliance with blood sampling was monitored by the secretariat. Clinicians were reminded each month of the patients for whom samples were due; those who had missed the previous visit were highlighted as urgent. The percentage compliance for each participating patient was calculated as the number of samples received divided by those expected x 100. The median time between samples was also calculated. Failure to achieve 50% of the expected samples was defined as poor compliance. Since the sensitivity to detect CEA rises in such patients was greatly reduced they were excluded from randomisation.

'Significant' Rises in CEA

A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on two successive occasions and one of the following conditions was also met: the CEA level was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the highest value was more than 7ng/ml above the lowest value ever recorded. If a 'significant' rise in CEA occurred, the record of the patient was reviewed at the Trials Centre and provided no evidence of suspected colorectal or other disease was recorded in the CRF, the patient was randomised either into an 'Aggressive' or 'Conventional' arm.

Figure 4: CEA algorithm

Randomisation

Patients were randomised equally between the two arms (1:1). Patients whose compliance was between 50 and 70% or whose immediate post-operative sample had not been received within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was also stratified by participating clinician. A block size of two was used in order to maintain as close a balance as possible between the two treatment arms.

If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise immediately by telephone from the trial centre and subsequently in writing and was requested to contact the patient urgently. Patients were informed of their situation including the fact that they had been randomised within the trial to undergo a second-look procedure. This was

then undertaken if the patient gave written informed consent. The surgeon carried out a full clinical work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g., change in smoking or drinking habit) and to identify any incurable distant spread. In the absence of these conditions the surgeon undertook a mini-laparotomy, proceeding to full laparotomy with macroscopic clearance of disease, should this be possible.
For patients randomised to the 'Conventional' arm no further action was taken; the clinician was neither informed that the CEA had risen nor that the patient had been randomised.

If at any stage a patient in the study developed clinical evidence of recurrent disease the clinician was at liberty to manage the patient according to usual practice. If the disease was in the abdomen and was thought to be treatable by a second-look operation with re-resection, this was acceptable. By the nature of the trial design, the clinician was blind as to whether such patients had been randomised to the 'Conventional' arm of the trial or had not been randomised because the CEA had failed to denote the presence of recurrent disease.

Second-Look Laparotomy
The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was detected all that was required prior to closure, was biopsy. Otherwise following a full excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis was undertaken. The liver was fully mobilised to determine whether any tumour was present. Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then carried out with the objective of total extirpation of all recurrence. Complete data recording of the procedure along with the results of the histology of all potentially involved sites was required by the trial's office.

For patients in whom a radical resection was achieved after second-look surgery (motivated either on clinical information or because the patient had been randomised to the 'Aggressive' arm) the follow-up schedules for clinical examination and blood sampling reverted to those following the primary operation. However, for patients randomised to the 'Aggressive' arm, clinicians were immediately notified of any further CEA levels above 10ng/ml.

Death
Every patient registered onto the study was 'flagged' with the Office of Population Censuses and Surveys (now ONS) who provide automatic notification of date of death. This enabled the trial centre to receive certified cause of death for all patients.

Trial oversight
A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not entering patients into the trial was asked to review the data after the first 100 patients had been randomised, which occurred in January 1988, and again after 200 patients had been randomised in February 1993. At this point it was recommended by the Data Monitoring Committee that the trial stopped since it was very unlikely that any clinically important advantage would be demonstrated for patients undergoing second-look surgery.

Methods of the RIAT process

The data

The RIAT restorative authors had been warned by the statisticians called in to look at the data in 2003-4 that "the databases were corrupted with key variables no longer abstractable".(37;38) We found that the data on paper and on file were accessible and we had no reason to doubt the veracity of individual items. We found that the electronic files had numerous problems with formatting which made the files on the 1447 individual patients difficult to handle but that the data entries were not themselves corrupted.

One of the RIAT restorative authors (KM) had worked in the trials units during the time the CEA Trial data were being accrued and knew the systems in use and their changes but was not directly involved in this trial at any stage.

The questions raised and the problems encountered, were resolved as follows:

- The codes indicating that a patient had met the criteria for CEA elevation and whether they were randomised to 'active' or 'Conventional' arm were preserved and tallied with the number in the 1994 manuscript.(32)

- There were variations in the way dates were recorded in the database. There had been migrations of data from a 'Prime' server using 'Universe' to 'Excel' and the interpretation of the present authors, with information from contemporary witnesses was that in undertaking the task operators did not always correctly specify these data as 'dates' when importing, and/or allowed them to be converted to American date formats. These errors prevented calculations and would have defeated running a survival analysis without correction of the file entries. The dates were however visually readable and not 'corrupt'. Some could be corrected by running current versions of software. Others were manually corrected by re-entering them in a Microsoft date format. Paper records were available to resolve uncertainties.

- The next problem was in linking these three groups of patients (randomised to 'Aggressive', randomised to 'Conventional' and not randomised) to the dates for survival analysis. Individual patients were uniquely identified in the files by seven digit strings to which letters had been added at the beginning and end, possibly for trial administrators' checklists or subgroup identification. Once we had established that the initial and terminal letters were redundant for analysis of the primary endpoint, we were able to write code to restore the seven digit strings.

- It was evident that the seven digits did not represent a simple sequence but certain positions identified particular characteristics, such as participating centre. We recognised a consistent pattern of mismatch in the fourth digit, a zero in one file was an 8 in the other with all other digits remaining the same. It was suggested to us that the fourth digit replacement was used to identify patients suitable for *post hoc* subgroup analyses but no documentation was found to confirm this. By checking back to the dates of birth we were able to confirm that this systematic correction resolved the problem and most of the data were then usable.

- By ranking all the data in the paired files for line by line visual inspection residual discrepancies were identified. Scrutinising the digit strings allowed for seven of the remaining eight pairs to be reconciled and verified on dates of birth. We failed to resolve only one out of 1447 records in each file. This patient had not been randomised.

- Inspection of the accrual of death dates was discontinuous for a couple of years suggesting a lapse in either recovery or entry. The current trials centre obtained permission to re-run the Office for National Statistics (ONS) search in July 2012.

In summary, we identified several problems but they were systematic and not random (we would not use the value laden word 'corrupted'). We were able to rectify the formatting errors and verify that the data used for our analysis were correct. The Kaplan Meier analysis was re-run.

Results

The original main results 1994

The study opened to recruitment in November 1982 and was closed by the Working Party, on the acceptance of a recommendation from the Data Monitoring Sub-committee, on 17th February 1993. During this period 1,447 patients were registered by 73 participating clinicians in 58 hospitals in the United Kingdom. Of these 39 (2.7%) were deemed ineligible since their CEA did not fall below 10 ng/ml by six weeks after surgery. A further 173 patients were excluded from analysis; four did not have a confirmed diagnosis of adenocarcinoma, 6 were considered unfit for continued monitoring, 4 had a previous and 1 a simultaneous non-colorectal malignancy, 2 had metastatic disease, and 156 (10.8%) never complied with the requirement for monthly blood sampling or only did so for 3 months or less.

Figure 5 paper records of the CEA results

Of 1,235 patients who continued in the trial, 80% achieved a greater than 60% compliance with blood sampling, whilst 12.5% registered between 40-59% of the required samples and only 7.5% had compliance of less than 40% The majority of randomisations (160/216; 74%) were prior to the second anniversary of the primary diagnosis. Three patients randomised had prior recurrent (2) or metachronous (1) disease detected clinically, without a rise in CEA and were operated upon.

Two hundred and sixteen patients developed a 'significant' rise in CEA and as no recurrent disease had been recorded at their latest trial follow-up, they were randomised by the Trial Office (108 to each arm). The median time from primary surgery to randomisation was 403 days, (range 103 to 1754) with no statistical difference between the two groups.(32)
The characteristics of patients in the two groups are given in Table 1.

Table 1

	Aggressive N=108	Conventional N=108
Sex male (%)	60(56%)	68(63%)
Age years, median and range	64 (33-75)	62 (35-75)
Pathological stage	N(%)	N(%)
Dukes' A	5 (4.6)	5 (4.6)
Dukes' B	46 (42.6)	49 (45.4)
Dukes' C[1]	36 (33.3)	38 (35.2)
Dukes' C[2]	17 (15.7)	10 (9.3)
Missing	4 (3.7)	6 (5.6)

The stage mix of 980 patients who were eligible for inclusion in the randomised trial but who did not have a CEA rise as defined was Dukes' A 15.1%, B 55.2%, C1 23.3%, C2 6.4%.

Of the patients randomised to the 'Aggressive' arm 83 (77%) had recurrent cancer identified and 62 (57%) patients had 'second-look' surgery. In patients randomised to the 'Conventional' arm 89 (82%) had developed recurrent disease by the date of analysis. In these 26 (24%) second-look procedures were undertaken. By February 1993, 91/108 in the the 'Aggressive arm' had died and 88/108 patients had died in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37).(32) It was considered by the data monitoring committee to be "highly unlikely that any survival advantage would be demonstrated for patients undergoing second-look surgery". This was communicated to the chief investigator.

RIAT restoration and updated survival analysis

The data were restored by the RIAT authors for 1446 of 1447 patients to the extent that the RIAT authors were confident of their dates of birth, death and whether they met criteria for entry into the controlled trial and then to which arm they were allocated.

The electronic records were intact with respect to the identity of the patients, which patients had reached the criteria for randomisation, and the trial arm to which they had been randomly allocated for all 216 patients who were randomised. The sex, age, primary site and Dukes' stage as recorded in the 1994 manuscript are shown in Table 1.

Certification of death was obtained from ONS on behalf of the RIAT restorative authors for 204 of 216 randomised patients who died between 17/10/1983 and 08/09/2011. There were equal numbers of patients in the two arms (108) and equal numbers of death dates were retrieved (102). We also have dates of death in 862 of the 1230 patients who were not randomised. Kaplan Meier analysis in these three groups is shown in Figure 6, showing survival of the 1230 participants who entered the trial but were not randomised and the 108 participants randomised into each arm.

Figure 6 Kaplan Meier analysis

The lead time conferred by CEA monitoring, defined as the median time to clinically detected disease for patients randomised to the 'Conventional' arm, was 323 days (95% confidence interval (CI) 203-443). This analysis included censored observations on 23 patients, however only five of these had a censored time less than the lead time. It was

regarded as unlikely, therefore, that the lead time would decrease as further events occur. The analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs 70% at a year. The RIAT authors did not repeat this analysis.

Discussion

We have restored data sufficient to achieve the primary outcome of interest as specified by the CEA trialists:

> "Does a policy of CEA-prompted second-look surgery following 'curative' resection of colorectal cancer produce a decrease in morbidity and mortality due to tumour recurrence, despite sequelae of second look surgery?"

The answer is that acting on CEA elevation by second-look surgery did not reduce mortality compared with patients in whom similar CEA elevation remained unknown. This negative finding led to the closing of the trial in 1994(2;24) and we confirm it here. There was small non-significant excess of deaths in the 'Aggressive' arm. The burden of morbidity attributable to the greater number of investigations and operations was not captured by the trial protocol nor indeed the 'needless anxiety' which concerned Moertel(23) and the authors of the CEA trial protocol.(1)

The second planned analysis was to obtain an accurate picture of the 'lead time' produced by CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up patients considerably sooner than the clinical methods available at the time by 11 months (95% CI 7-14 months).

CEA monitoring for the purpose of early detection of asymptomatic cancer is currently recommended at least every 6 months in the first three years. In addition a minimum of two CT scans are recommended in the first three years.(39) The FACS trial, recently reported, has also shown no survival advantage from CEA monitoring compared with minimum follow-up.(40) More operations were performed with 'curative intent' for recurrent cancer in those having more intensive monitoring and there were more deaths (18.2%[164/901] vs 15.9% [48/301]; difference, 2.3%; 95%CI, −2.6%to 7.1%). These results are similar to the findings in the CEA trial. Although the phrase 'curative intent' occurs about 40 times in the manuscript, better survival was not achieved with any of the three monitoring schedules compared with minimum follow-up.

The third and fourth intentions set out by the CEA trialists were c) to obtain further data relating CEA levels to tumour histology and topography and d) a large data base on the natural history of colorectal cancer. Multiple CEA assay results exist in the data we hold for 1446 patients and it would be possible to link these to survival as a result of the RIAT restorative work.

With respect to the natural history of colorectal cancer although we trust the death certification data for the date of death it has been shown that "at least a third of all death certificates are likely to be incorrect"(41). No doubt aware of this and seeking much more detailed information, the CEA Trialists had asked for detailed post-mortem examinations. It appears that it was disagreement concerning explanatory analyses which contributed to the failure to publish the primary outcome of interest.(32) The purpose of such analyses would

be to discover subsets of patients in whom there was a benefit from the intervention under evaluation and to thus determine the characteristics of patients in whom the intervention might have had a beneficial effect by analysis of mediators and moderators.(42) There is a general objection to this exercise because it can lead to spurious associations.(43;44) Furthermore when there is no overall benefit found, as in the CEA Second-Look Trial, any subgroup(s) where there is a positive association between intervention and outcome must be balanced by one or more other groups where there was net harm. The methods section of the 1994 manuscript states 'Subgroup analyses have been performed to address specific issues but these need to be interpreted with appropriate caution.'(32) In the event no completed subset analyses were in the 1994 paper and the closing notes between the authors are on the matter of a subset analysis. We have not attempted any in restoring the trial.

The answer to the primary research question was clear in 1993 and was the explicit reason for stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery had been missed and in the absence of benefit there was net harm being done to the patients. The forms of second look surgery now widely practiced in colorectal cancer are liver and lung resection of metastases.

- Full mobilisation of the liver at second-look laparotomy was included in the CEA Trial protocol. Hepatic resection has entered routine practice based on observational data(45) and an opportunity to do a randomised trial, for which a power calculation was proposed in 1992 from the Mayo Clinic(46) was not taken.(25)
- Two patients had a thoracotomy prompted by CEA elevation. Pulmonary metastasectomy for colorectal cancer is, after primary lung cancer, the second commonest thoracic cancer operation and is the subject of an ongoing randomised controlled trial.(47)

The CEA Trial findings have been corroborated by the larger FACS trial. If the CEA trial results had been made available in 1994, and there is no evident reason why they should not have been, a more critical scrutiny of the evidence base that was used to bring liver and lung metastasectomy into practice. (25;30) might have been undertaken. The CEA Trial was a well-conceived and meticulously executed randomised trial and we hope that publishing it now more than twenty years after its completion will indicate the possibility of more randomised trials in surgery.(48)

Legends

Figure 1. The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.(1)

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.(15)

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.(1)

Figure 4. Decision making algorithm for CEA to trigger second-look surgery.(15)

Figure 5. Flow chart of enrolled and ultimately randomised patients. 'Blind' in the bottom left box means that the clinical teams were unaware of the elevated CEA discovered and were unaware that the patients have been randomised. They were indistinguishable amongst the 1230 non-randomised patients who were being followed-up. (See Figure 6)

Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from Office for National Statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230) Some would have had clinically evident early recurrence precluding randomisation. The initial plateau is an illustration of a death free interval(49) or "immortal time bias"(50) Patients in prospective studies may have a built in obligatory survival time from some starting point in order to attain the requirements to be included in the data set. This is an artefact but may be absorbed into survival time adding to and not readily distinguished from survival time attributed to treatment.

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Contributor statement
TT instigated the recovery of the data, worked on the database recovery described in the manuscript and wrote the first and edited the final version of the manuscript.
KM navigated the data files and worked on the database recovery described in the manuscript.
FF performed the analysis of the recovered data and the presentation of the analysis.
RCGR negotiated access to the data and with TT contacted and interviewed the members of the original trial team.
All authors have read and contributed to successive iterations of the manuscript and approve the submitted version.

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Data sharing
We are prepared to share the anonymised electronic data in our possession. The chief investigator (JMAN) and the chair of data monitoring committee (MB) provided a signed agreement on 21st February 2014 to allow access to the archived paper records and electronic files (held by UCLCTC) at the discretion of the RIAT authors. CEA Survival data for two randomised and one non randomised groups can be accessed in the Dryad data repository: doi:10.5061/dryad.s3p05

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None of the authors have conflicts of interest.

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Title

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

Tom Treasure[1]
Kathryn Monson[2]
Francesca Fiorentino[3]
Christopher Russell

[1]Clinical Operational Research Unit, University College London

[2] Sussex Health Outcomes, Research & Education in Cancer (SHORE-C)
University of Sussex

[3] Department of Cardiothoracic Surgery, NHLI, Imperial College London

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Contributor statement

TT instigated the recovery of the data, worked on the database recovery described in the manuscript and wrote the first and edited the final version of the manuscript.
KM navigated the data files and worked on the database recovery described in the manuscript.
FF performed the analysis of the recovered data and the presentation of the analysis.
RCGR negotiated access to the data and with TT contacted and interviewed the members of the original trial team.
All authors have read and contributed to successive iterations of the manuscript and approve the submitted version.

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Data sharing

We are prepared to share the anonymised electronic data in our possession. The chief investigator (JMAN) and the chair of data monitoring committee (MB) provided a signed agreement on 21st February 2014 ~~have agreed~~ to allow access to the archived paper records and electronic files (held by UCLCTC) at the discretion of the RIAT authors~~.~~.

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Comment [T1]: [Editor: we will send this written agreement.]

Acknowledgments

The RIAT authors are grateful to Jonathan Ledermann, Director of the Cancer Research UK & UCL Cancer Trials Centre, University College London, (where the CEA files were stored) and Sharon Forsyth for her assistance in accessing the CEA trial data and updating the Office

of National Statistics records for death registration. We acknowledge the assistance of Sonya Crowe of UCL's Clinical Operational Research Unit is technical aspects of restoring the electronic files to a usable state. The RIAT authors also met with the following persons who were members of the 1982 Working Party at the Cancer Research Campaign Clinical Trials Centre (CRC CTC) King's College Hospital Medical School, London and/or were listed as contributors in the 1994 manuscript from the CRC CTC at the Rayne Institute, 123 Coldharbour Lane, London SE5 9NU: M Baum, RHJ Begent, H Ellis, J Houghton, M Irving, CA Lennon, JMA Northover, WW Slack and CB Wood. ~~We are grateful to them for frank discussions concerning the progress of the study and the factors leading to its abandonment.~~ We are particularly grateful to JMAN who met with TT and RCGR at the Royal Society of Medicine in London on Monday 10th February 2014 and read and commented on a near final version of the manuscript and agreed our interpretation of the trial results. The principle findings reported here corroborate those in his letter to JAMA in 1994. JMAN helped us understand the sequence of events leading to the closure of the trial and subsequent lapse in writing up the full report. ~~We acknowledge the assistance of Sonya Crowe of UCL's Clinical Operational Research Unit is technical aspects of restoring the electronic files to a usable state.~~

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None of the authors have conflicts of interest.

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Abstract

Objectives: in patients who have undergone a potentially curative resection of colorectal cancer does a 'second-look' operation to resect recurrence, prompted by monthly monitoring of carcinoembryonic antigen, confer a survival benefit?

Design: a randomised controlled trial recruiting 1982 to 1994 recovered under the RIAT initiative (Restoring Invisible and Abandoned Trials).

Setting: 58 hospitals in the United Kingdom and Europe.

Participants: from 1982 to 1993, 1447 patients were enrolled. Of these 216 met the criteria for CEA elevation and were randomised to 'Aggressive' or 'Conventional' arms.

Interventions: 'second-look' surgery with intention to remove any recurrence discovered.

Primary outcome measure: survival.

Results: by February 1993, 91/108 patients had died in the 'Aggressive arm' and 88/108 in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37). By 2011 a further 25 randomised patients had died. Kaplan Meier analysis showed no difference in long-term survival.

Conclusions: the trial was closed in 1993 following a recommendation from the Data Monitoring Committee that it was highly unlikely that any survival advantage would be demonstrated for CEA prompted second-look surgery. This conclusion was confirmed by repeat analysis of survival times after twenty years.

International Standard Randomised Controlled Trial Number ISRCTN76694943 Date applied 1st July 2001 and recorded as 'completed'

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Strengths and limitations of this study

- The CEA Second-Look Trial was a well-planned and carefully executed study with a clear question and a well-defined outcome of interest.
- Second-look surgery prompted by the best available indicator of recurrence at the time conferred no survival advantage.
- A further strength, and a reason to publish this trial now, is that it shows that randomised trials in surgery can be done and that the result may be contrary to the beliefs and expectations of practitioners based on their uncontrolled observations.

A limitation is that present day means of non-invasive detection of asymptomatic recurrence were not available at the time of the CEA Second-Look Trial. A recently reported randomised controlled trial (FACS) in which CEA and/or CT were compared with minimum follow-up showed no survival advantage associated with earlier detection.

Comment [T2]: [Editor: the form of trial we suggested here has now been reported and feel there is no alternative but to replace the comment with this update.]

Introduction

The Working Party of the Carcinoembryonic antigen (CEA) Second-Look Trial set the scene for their trial in their protocol in 1982(1) The principle finding, that CEA monitoring to detect asymptomatic recurrence was not associated with improved survival, was announced in a letter to the Journal of the American Medical Association in 1994 by Northover, the then Chief Investigator.(2) The writing of the trial for publication lapsed. We here report the trial under the RIAT initiative (Restoring invisible and abandoned trials).(3;4)

It had been ~~was~~ observed during the 1970s that the outlook for patients with colorectal cancer was not good. Only one in four patients survived for five years after diagnosis and radical surgery was observed to be curative in under half of patients (5)~~(1)~~. Results had not improved in several decades.(1;6;7)~~(2–4)~~. Refinements in primary operative techniques had not made a difference(8)~~(5)~~ and it was considered unlikely that technical modifications would lead to improvement in survival following surgery.(5;6)~~(1;2)~~ Routine surgical follow-up had not led to further surgery being shown to be beneficial: clinical evidence of recurrence usually meant that the tumour would be unresectable at second-look laparotomy.(9)~~(6)~~ The published experience of members of the ~~Carcinoembryonic antigen (CEA) Second-Look Trial~~ Working Party who developed and launched the trial ~~development group~~ was that of 180 patients, followed up from six months to 15 years, with a total of 2319 out-patient clinic visits, only one patient could be considered to have had a potentially curative second-look operation.(10)~~(7)~~ They concluded that to re-resect with prospect of benefit, recurrence had to be detected before it was clinically evident(1)~~(4)~~ but more pro-active clinical follow-up of asymptomatic patients by three monthly sigmoidoscopy, barium enema and chest X-ray (the methods available at the time) had failed to show improvement in 5-year survival.(11)~~(8)~~ Nevertheless, there had been several reports of 30% five-year survival in selected patients after radical resection of recurrent cancer(7;12;13)~~(3;9;10)~~ and resection was believed to sometimes lead to "cure".(7;12-14)~~(3;9–11)~~

Improving detection and treatment of recurrent disease: the context in1982

The trial development group considered the evidence available at the time for methods of detecting recurrence early and a founding principle of the CEA Second-Look Trial was that early detection of recurrent tumour would only be justifiable if further treatment offered the prospect of benefit to the individual patient.(1)~~(4)~~ The evidence available to the trial working party in 1982 is outlined below.

Figure 1 Working Party membership

The Wangensteen Approach:

During the 1950s the systematic use of a policy-based second operation was reported. Patients at high risk of recurrence (those with Dukes' Stage C tumours) were re-operated on at 6-monthly intervals, resecting recurrence when found, until they were 'tumour free'. If cancer had been found the patients were scheduled for 3rd and more "looks", up to six further abdominal operations, "before the abdomen was free of cancer". Once a patient had undergone a negative laparotomy, no more surgery was recommended. Sixty-four patients with colon or rectal cancer were managed in this way. In 35 (55%) of them the "second-look" laparotomy was negative for the discovery of recurrent cancer, seven of whom subsequently had clinical recurrence. There were four (6%) operative deaths.(15)~~(12)~~ The

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~~CEA~~ Working Party ~~trialists~~ concluded that this 'blanket second-look' policy might have produced some "cures" but entailed high rates of negative laparotomy and an unacceptable operative mortality rate.(1)~~(4)~~

Figure 2 from Wangensteen 1954

The CEA-prompted Second-Look Approach

CEA had been shown to detect recurrence of colorectal cancer following surgery.(16-21)~~(13-18)~~ CEA rose, on average, four months prior to clinical evidence of recurrence(17)~~(14)~~ and there were reports of the use of serial serum carcinoembryonic antigen (CEA) assays to detect asymptomatic recurrences in the belief that curative resection would be possible more frequently.(16-18)~~(13-15)~~ Several groups used CEA in this way, and found low false positive rates(9;22)~~(6;19)~~ and the resectability rate of the recurrence was higher than when clinical criteria were used to prompt re-operation.(9)~~(6)~~ In the largest published experience of CEA in a post-operative monitoring role(9;16)~~(6;13)~~ recurrent tumour, which was resectable, was found in 70% in whom re-operation was prompted by a rise in the serum CEA compared with a quarter of patients undergoing second-look laparotomy prompted by clinical indications. Others had not found CEA to be useful in this post-operative monitoring role. Even if efficacy of CEA detected recurrence was accepted, there was still the unresolved question of effectiveness: if more patients were detected and there were more instances of resectable recurrence, did that lead to better survival and patient benefit? The conflicting interpretations of observational data resulted in calls for trials(16;22;23)~~(13;19;20)~~ including one within a 1981 NIH Consensus Statement.(21)~~(18)~~

The objective of the CEA Second-Look Surgery Trial was to determine whether, following potentially curative primary surgery for colorectal cancer, mortality could be decreased by a policy of second-look surgery prompted by rising serum carcinoembryonic antigen (CEA). The trial ran from 1982 to 1993. The main result, that there was no survival advantage, was reported in 1994 to the British Oncological Association(24)~~(21)~~ and was published in a letter to the Journal of the American Medical Association.(2)~~(22)~~

Detection and reoperation for asymptomatic colorectal cancer recurrence has since become routine both in the form of hepatic resection(25)~~(23)~~ and pulmonary metastasectomy(26)~~(24)~~ but without evidence from controlled trials for either practice.(27;28)~~(25;26)~~ When doubts were raised about the security of the evidence in the British Medical Journal in 2007(27)~~(25)~~ a general belief existed that randomised controlled trials of the effectiveness of resection of liver or lung metastases were not possible and were not needed. These paired beliefs are brought into question by the previously unpublished CEA Second-Look Trial: a randomised trial had been ~~was~~ done and the presumed benefit of surgery for cancer recurrence was not seen.(2;24)~~(21;22)~~

Closure of the trial in 1993 and gaining access to the data in 2011

The RIAT restorative authors had been involved in various studies related to surgery for disseminated colorectal cancer(27;29;30)~~(25;27;28)~~ including a conundrum as to whether discovery of an elevated CEA assay should prompt, ~~—~~or be considered a contra-indication to, ~~-~~ pulmonary metastasectomy.(31)~~(29)~~ We knew the CEA trial had ~~to have~~ been recruiting ~~enrolling patients~~ in the 1980s but when we searched the literature for the result of the trial

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found nothing later than 1994.(2;24)~~(21;22)~~ In 2009 we contacted the chief investigator of the trial at the time of its closure (JMAN) and the present director of the University College London Cancer Trials Centre (JAL). We were informed that the data were irretrievably lost. However, staff at UCL CTC were aware that CEA trial data were still in the department and after further enquiries RCGR ~~the RIAT authors~~ gained access to anonymised electronic data in 2011. The process of data restoration is described later. It was agreed that the trial would be published as part of 'Restoring invisible and abandoned trials'(RIAT).(3;4)

Amongst the documents made available to the RIAT restorative authors were listed the members of the trial development group in the 1982 protocol(1)~~(4)~~ and the contributors to the 1994 manuscript.(32)~~(30)~~ None of these individuals expressed an interest in resuming work on the trial or were in a position to do so. When we contacted them later to share the restored data with them no one raised any objection but on the contrary encouraged us to publish their findings.

Methods: trial intent and design

The recruitment intentions and the trial protocol as presented here are essentially as written in the manuscript prepared in 1994 with the full intention of publishing the trial.(32)~~(30)~~ The text has been edited by the RIAT authors but no new material has been introduced.

The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years and to follow them for five years. The study was specifically designed with late randomisation in order to maximise statistical power. It was originally intended to recruit 2,000 patients with the anticipation that about 25% would show a CEA rise as the first evidence of possible recurrence. This number would have provided 95% power to detect an improvement in two year survival from the second-look procedure from 25% to 55% at α=0.05. The protocol stated that for the trial to be stopped prematurely very stringent levels of significance ($p<0.001$) would be used. Analyses of the randomised groups were to be by Kaplan-Meier lifetables and the logrank test on 'intention to treat'.(32)

Their intentions were explicitly set out as follows in 1981:(33)~~(31)~~

'So far as society in general is concerned, if CEA monitoring is shown to be of benefit in this study, then it will be a powerful incentive to the great majority of surgeons who see no obvious advantage in routine CEA monitoring to adopt the technique; as colorectal cancer is the second commonest killing cancer in the Western world, the benefits would thus be enormous. If, however, CEA monitoring is shown to be of no long term therapeutic value then it should cease to be used in its presently available form, and patients will thereby be spared the 'needless anxiety' of premature knowledge of their impending death.(23)~~(20)~~'

The CEA trial design was devised so that clinical follow-up would remain unbiased, and allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent colorectal cancer. After potentially curative surgery for colorectal cancer, all eligible patients were to be monitored identically using conventional clinical follow-up together with regular CEA assay, performed centrally. Clinicians would not be informed of the result. When a 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm,

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the clinician would immediately be informed of the CEA rise so that the patient could be urgently screened to exclude widespread metastatic disease or a non-malignant cause for the CEA rise. If neither was found, and the patient was medically fit for operation, the protocol required second-look surgery to locate and remove any treatable recurrence. In the case of patients in the 'Conventional' arm, the clinician would not be informed of the 'significant' CEA rise nor of the fact that they had been randomised to not have the CEA rise revealed.

The primary outcome was survival based on death certification through the Office of Population Censuses and Surveys (OPCS) (now called the Office for National Statistics (ONS)). No subset analyses were planned.

The intention as stated in the protocol was that the trial would produce:

a) a definitive answer concerning the effectiveness of CEA-prompted second-look surgery to improve survival
b) an accurate picture of the 'lead time' produced by CEA compared to clinically indicated second-look surgery
c) further data relating CEA levels to tumour histology and topography, and
d) a large data base on the natural history of colorectal cancer.(1)~~(4)~~

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The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements give no indication as to the precise nature of analyses that might follow and are regarded as opportunities for explanatory subset analyses which were not in the event carried out.

Methods: the conduct of the trial 1982 to 1993

The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical Trials Centre at King's College Hospital. CEA assays were performed using a radioimmunoassay technique at a single centre at Charing Cross Hospital.

Selection of patients

All patients up to the age of 76 who had undergone a potentially curative resection for adenocarcinoma of the colon or rectum and who were fit and willing to adhere to the post-operative monitoring routine were eligible for the study. Patients were excluded if there was evidence of incurable distant spread, either pre-operatively or during the primary operation, or if the CEA level failed to return to the normal range (<10 ng/ml) within six weeks of primary surgery. Patients who had previously received treatment for other types of cancer, apart from basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix adequately cone biopsied, were excluded from the study.

Management of the primary tumour

A pre-operative blood sample for CEA assay was taken from all patients with suspected colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. This was a pragmatically designed study so surgeons were at liberty to use their normal operative technique and to employ pre- or post-operative radiotherapy or adjuvant chemotherapy as was seen fit, however they were asked to remain consistent regarding the treatment used for any particular type of disease. If at laparotomy, a potentially curative resection was performed and subsequent histology confirmed the diagnosis of adenocarcinoma, the patient was given a full explanation of the study and could be registered.

Consent

The 1982 protocol includes a consent form (Consent form ~~1~~A) to be completed at registration and a further form (Consent form ~~2~~B) for patients who were randomised to a 'Second-Look Laparotomy'. There was a ~~and a~~ protocol amendment in which the word 'cancer' is to be replaced throughout by 'a growth'.(1)~~(4)~~

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Baseline data

The surgeon carried out investigations to detect the presence of synchronous colorectal tumours (both benign and malignant) and to exclude occult liver spread; (usually barium enema examination and ultrasound or CT scan of the liver). In addition, factors that could give raised CEA levels in the absence of recurrent colorectal cancer, such as chronic lung disease, cirrhosis, chronic pancreatitis, and chronic renal failure were excluded by clinical questioning, chest x-ray, liver function tests, blood urea and electrolytes. Smoking habits and alcohol consumption were also recorded as heavy smoking or drinking, or a change in these habits, can influence CEA levels.

Figure 3: Trial flow diagram

Monitoring of Patients

Clinical follow-up of all patients continued in an identical manner (three monthly for the first two years and six monthly for the next three years) whilst blood for CEA assay was drawn monthly for the first three years and three monthly for the next two years. If the patient remained well and the CEA was within normal limits as defined by a pre-tested algorithm, monitoring continued according to the schedule.

CEA assay

Ten mls of whole blood were taken from each patient. The serum was separated and sent to the Trials Centre in special plastic phials. After logging receipt, the samples were forwarded to the Medical Oncology Department at Charing Cross Hospital for assay. The results were returned to the Trials Centre for recording and action if appropriate. This centralised system ensured that all participating clinicians were kept blind to the CEA results for their patients. It also ensured quality control of the CEA assay as there was no possibility of inter-laboratory variation.

Serum CEA values were measured by double antibody radioimmunoassay.(34-36)~~(32-34)~~ A bank of serum samples has been retained at -20°C.

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Monitoring assay compliance pre-randomisation

Throughout the trial, compliance with blood sampling was monitored by the secretariat. Clinicians were reminded each month of the patients for whom samples were due; those who had missed the previous visit were highlighted as urgent. The percentage compliance for each participating patient was calculated as the number of samples received divided by those expected x 100. The median time between samples was also calculated. Failure to achieve 50% of the expected samples was defined as poor compliance. Since the sensitivity to detect CEA rises in such patients was greatly reduced -they were excluded from randomisation.

'Significant' Rises in CEA

A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on two successive occasions and one of the following conditions was also met: the CEA level was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the highest value was more than 7ng/ml above the lowest value ever recorded. If a 'significant' rise in CEA occurred, the record of the patient was reviewed at the Trials Centre and provided no evidence of suspected colorectal or other disease was recorded in the CRF, the patient was randomised either into an 'Aggressive' or 'Conventional' arm.

Figure 4: CEA algorithm

Randomisation

Patients were randomised equally between the two arms (1:1). Patients whose compliance was between 50 and 70% or whose immediate post-operative sample had not been received within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was also stratified by participating clinician. A block size of two was used in order to maintain as close a balance as possible between the two treatment arms.

If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise immediately by telephone from the trial centre and subsequently in writing and was requested to contact the patient urgently. Patients were informed of their situation including the fact that they had been randomised within the trial to undergo a second-look procedure. This was

then undertaken if the patient gave written informed consent. The surgeon carried out a full clinical work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g., change in smoking or drinking habit) and to identify any incurable distant spread. In the absence of these conditions the surgeon undertook a mini-laparotomy, proceeding to full laparotomy with macroscopic clearance of disease, should this be possible.
For patients randomised to the 'Conventional' arm no further action was taken; the clinician was neither informed that the CEA had risen nor that the patient had been randomised.

If at any stage a patient in the study developed clinical evidence of recurrent disease the clinician was at liberty to manage the patient according to usual practice. If the disease was in the abdomen and was thought to be treatable by a second-look operation with re-resection, this was ~~perfectly~~ acceptable. By the nature of the trial design, t~~T~~he clinician was blind as to whether such patients had been randomised to the 'Conventional' arm of the trial or had not been randomised because the CEA had failed to denote the presence of recurrent disease.

Second-Look Laparotomy
The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was detected all that was required prior to closure, was biopsy. Otherwise following a full excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis was undertaken. The liver was fully mobilised to determine whether any tumour was present. Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then carried out with the objective of total extirpation of all recurrence. Complete data recording of the procedure along with the results of the histology of all potentially involved sites was required by the trial's office.

For patients in whom a radical resection was achieved after second-look surgery (motivated either on clinical information or because the patient had been randomised to the 'Aggressive' arm) the follow-up schedules for clinical examination and blood sampling reverted to those following the primary operation. However, for patients randomised to the 'Aggressive' arm, clinicians were immediately notified of any further CEA levels above 10ng/ml.

Death
Every patient registered onto the study was 'flagged' with the Office of Population Censuses and Surveys (now ONS) who provide automatic notification of date of death. This enabled the trial centre to receive certified cause of death for all patients.

Trial oversight
A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not entering patients into the trial was asked to review the data after the first 100 patients had been randomised, which occurred in January 1988, and again after 200 patients had been randomised in February 1993. At this point it was recommended by the Data Monitoring Committee that the trial stopped since it was very unlikely that any clinically important advantage would be demonstrated for patients undergoing second-look surgery.

Methods of the RIAT process

The data

The RIAT restorative authors had been warned by the statisticians called in to look at the data in 2003-4 that "the databases were corrupted with key variables no longer abstractable".(37;38)~~(35;36)~~ We found that the data on paper and on file were accessible and we had no reason to doubt the veracity of individual items. We found that the electronic files had numerous problems with formatting which made the files on the 1447 individual patients difficult to handle but that the data entries were not themselves corrupted.

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One of the RIAT restorative authors (KM) had worked in the trials units during the time the CEA Trial data were being accrued and knew the systems in use and their changes but was not directly involved in this trial at any stage.

The questions raised and the problems encountered, were resolved as follows:

- The codes indicating that a patient had met the criteria for CEA elevation and whether they were randomised to 'active' or 'Conventional' arm were preserved and tallied with the number in the 1994 manuscript.(32)~~(30)~~

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- There were variations in the way dates were recorded in the database. There had been migrations of data from a 'Prime' server using 'Universe' to 'Excel' and the interpretation of the present authors, with information from contemporary witnesses was that in undertaking the task operators did not always correctly specify these data as 'dates' when importing, and/or allowed them to be converted to American date formats. These errors prevented calculations and would have defeated running a survival analysis without correction of the file entries. The dates were however visually readable and not 'corrupt'. Some could be corrected by running current versions of software. Others were manually corrected by re-entering them in a Microsoft date format. Paper records were available to resolve uncertainties.

- The next problem was in linking these three groups of patients (randomised to 'A~~a~~ggressive', randomised to 'C~~c~~onventional' and not randomised) to the dates for survival analysis. Individual patients were uniquely identified in the files by seven digit strings to which letters had been added at the beginning and end, possibly for trial administrators' checklists or subgroup identification. Once we had established that the initial and terminal letters were redundant for analysis of the primary endpoint, we were able to write code to restore the seven digit strings.

- It was evident that the seven digits did not represent a simple sequence but certain positions identified particular characteristics, such as participating centre. We recognised a consistent pattern of mismatch in the fourth digit, ~~-~~a zero in one file was an 8 in the other with all other digits remaining the same. It was suggested to us that the fourth digit replacement was used to identify patients suitable for *post hoc* subgroup analyses but no documentation was found to confirm this. By checking back to the dates of birth we were able to confirm that this systematic correction resolved the problem and most of the data were then usable.

- By ranking all the data in the paired files for line by line visual inspection residual discrepancies were identified. Scrutinising the digit strings allowed for seven of the remaining eight pairs to be reconciled and verified on dates of birth. We failed to resolve only one out of 1447 records in each file. This patient had not been randomised.

- Inspection of the accrual of death dates was discontinuous for a couple of years suggesting a lapse in either recovery or entry. The current trials centre obtained permission to re-run the Office for National Statistics (ONS) search in July 2012.

In summary, we identified several problems but they were systematic and not random (we would not use the value laden word 'corrupted'). We were able to rectify the formatting errors and verify that the data used for our analysis were correct. The Kaplan Meier analysis was re-run.

UCL CTC obtained updated death certification and supplied the data to the RIAT authors.

Results

The original main results 1994

The study opened to recruitment in November 1982 and was closed by the Working Party, on the acceptance of a recommendation from the Data Monitoring Sub-committee, on 17th February 1993. During this period 1,447 patients were registered by 73 participating clinicians in 58 hospitals in the United Kingdom and Europe. Of these 39 (2.7%) were deemed ineligible since their CEA did not fall below 10 ng/ml by six weeks after surgery. A further 173 patients were excluded from analysis; four did not have a confirmed diagnosis of adenocarcinoma, 6 were considered unfit for continued monitoring, 4 had a previous and 1 a simultaneous non-colorectal malignancy, 2 had metastatic disease, and 156 (10.8%) never complied with the requirement for monthly blood sampling or only did so for 3 months or less.

Figure 5 paper records of the CEA results

Of 1,235 patients who continued in the trial, 80% achieved a greater than 60% compliance with blood sampling, whilst 12.5% registered between 40-59% of the required samples and only 7.5% had compliance of less than 40% The majority of randomisations (160/216; 74%) were prior to the second anniversary of the primary diagnosis. Three patients randomised had prior recurrent (2) or metachronous (1) disease detected clinically, without a rise in CEA and were operated upon.

Two hundred and sixteen patients developed a 'significant' rise in CEA and as no recurrent disease had been recorded at their latest trial follow-up, they were randomised by the Trial Office (108 to each arm). The median time from primary surgery to randomisation was 403 days, (range 103 to 1754) with no statistical difference between the two groups.(32)~~(30)~~ The characteristics of patients in the two groups are given in Table 1.

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Table 1

	Aggressive N=108	Conventional N=108
Sex male (%)	60(56%)	68(63%)
Age years, median and range	64 (33-75)	62 (35-75)
Pathological stage	N(%)	N(%)
Dukes' A	5 (4.6)	5 (4.6)
Dukes' B	46 (42.6)	49 (45.4)
Dukes' C[1]	36 (33.3)	38 (35.2)
Dukes' C[2]	17 (15.7)	10 (9.3)
Missing	4 (3.7)	6 (5.6)

The stage mix of 980 patients who were eligible for inclusion in the randomised trial but who did not have a CEA rise as defined was Dukes' A 15.1%, B 55.2%, C1 23.3%, C2 6.4%.

Of the patients randomised to the 'Aggressive' arm 83 (77%) had recurrent cancer identified and 62 (57%) patients had 'second-look' surgery. In patients randomised to the 'Conventional' arm 89 (82%) had developed recurrent disease by the date of analysis. In these 26 (24%) second-look procedures were undertaken. By February 1993, 91/108 in the the 'Aggressive arm' had died and 88/108 patients had died in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37).(32)~~(30)~~ It was considered by the data monitoring committee to be "highly unlikely that any survival advantage would be demonstrated for patients undergoing second-look surgery". This was communicated to the chief investigator.

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RIAT restoration and updated survival analysis

The data were restored by the RIAT authors for 1446 of 1447 patients to the extent that the RIAT authors were confident of their dates of birth, death and whether they met criteria for entry into the controlled trial and then to which arm they were allocated.

The electronic records were intact with respect to the identity of the patients, which patients had reached the criteria for randomisation, and the trial arm to which they had been randomly allocated for all 216 patients who were randomised. The sex, age, primary site and Dukes' stage as recorded in the 1994 manuscript are shown in Table 1.

Certification of death was obtained from ONS on behalf of the RIAT restorative authors for 204 of 216 randomised patients who died between 17/10/1983 and 08/09/2011. There were equal numbers of patients in the two arms (108) and equal numbers of death dates were retrieved (102). We also have dates of death in 862 of the 1230 patients who were not randomised. Kaplan Meier analysis in these three groups is shown in Figure 6, showing survival of the 1230 participants who entered the trial but were not randomised and the 108 participants randomised into each arm.

Figure 6 Kaplan Meier analysis

The lead time conferred by CEA monitoring, defined as the median time to clinically detected disease for patients randomised to the 'Conventional' arm, was 323 days (95% confidence interval (CI) 203-443). This analysis included censored observations on 23 patients, however only five of these had a censored time less than the lead time. It was

regarded as unlikely, therefore, that the lead time would decrease as further events occur. The analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs 70% at a year. The RIAT authors did not repeat this analysis.

Discussion

We have restored data sufficient to achieve the primary outcome of interest as specified by the CEA trialists:

> "Does a policy of CEA-prompted second-look surgery following 'curative' resection of colorectal cancer produce a decrease in morbidity and mortality due to tumour recurrence, despite sequelae of second look surgery?"

The answer is that acting on CEA elevation by second-look surgery did not reduce mortality compared with patients in whom similar CEA elevation remained unknown. This negative finding led to the closing of the trial in 1994(2;24)~~(21;22)~~ and we confirm it here. There was small non-significant excess of deaths in the 'Aggressive' arm. The burden of morbidity attributable to the greater number of investigations and operations was not captured by the trial protocol nor indeed the 'needless anxiety' which concerned Moertel(23)~~(20)~~ and the authors of the CEA trial protocol.(1)~~(4)~~

The second planned analysis was to obtain an accurate picture of the 'lead time' produced by CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up patients considerably sooner than the clinical methods available at the time by ~~s~~11 months (95% CI 7-14 months).

CEA monitoring ~~is currently recommended~~ for the ~~is~~ purpose of early detection of asymptomatic cancer is currently recommended at least every 6 months in the first three years. In addition a minimum of two CT scans are recommended in the first three years.(39)~~(37)~~ The FACS trial, recently reported, has also shown~~ed~~ no survival advantage compared from CEA monitoring compared with minimum follow-up.(40)~~(38)~~ More operations were performed with 'curative intent' for recurrent cancer in those having more intensive monitoring and there were more deaths (18.2%[164/901] vs 15.9% [48/301]; difference, 2.3%; 95%CI, −2.6%to 7.1%). These results are similar to the findings in the CEA trial. Although the phrase 'curative intent' occurs about 40 times in the manuscript, longer survival is not evident.

The third and fourth intentions set out by the CEA trialists were c) to obtain further data relating CEA levels to tumour histology and topography and d) a large data base on the natural history of colorectal cancer. Multiple CEA assay results exist in the data we hold for 1446 patients and it would be possible to link these to survival as a result of the RIAT restorative work.

With respect to the natural history of colorectal cancer although we trust the death certification data for the date of death it has been shown that "at least a third of all death certificates are likely to be incorrect"(41)~~(39)~~. No doubt aware of this and seeking much more detailed information, the CEA Trialists had asked for detailed post-mortem examinations. It appears that it was disagreement concerning explanatory analyses which contributed to the failure to publish the primary outcome of interest.(32)~~(30)~~ The purpose of such analyses would be ~~is~~ to discover subsets of patients in whom there was a benefit from

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the intervention under evaluation and to thus determine the characteristics of patients in whom the intervention might have had a beneficial effect by analysis of mediators and moderators.(42)~~(40)~~ There is a general objection to this exercise because it can lead to spurious associations.(43;44)~~(41;42)~~ Furthermore when there is no overall benefit found, as in the CEA Second-Look Trial, any subgroup(s) where there is a positive association between intervention and outcome must be balanced by one or more other groups where there was net harm. The methods section of the 1994 manuscript states 'Subgroup analyses have been performed to address specific issues but these need to be interpreted with appropriate caution.'(32) In the event no ~~There were~~ no completed subset analyses were in the 1994 paper and the closing notes between the authors are on the matter of a subset analysis. W~~and w~~e have not attempted any in restoring the trial.

The answer to the primary research question was clear in 1993 and was the explicit reason for stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery had been missed and in the absence of benefit there was net harm being done to the patients. The forms of second look surgery now widely practiced in colorectal cancer are liver and lung resection of metastases.

- Full mobilisation of the liver at second-look laparotomy was included in the CEA Trial protocol. Hepatic resection has entered routine practice based on observational data(45)~~(43)~~ and an opportunity to do a randomised trial, for which a power calculation was proposed in 1992 from the Mayo Clinic(46)~~(44)~~ was not taken.(25)~~(23)~~
- Two patients had a thoracotomy prompted by CEA elevation. Pulmonary metastasectomy for colorectal cancer is, after primary lung cancer, the second commonest thoracic cancer operation and is the subject of an ongoing randomised controlled trial.(47)~~(45)~~

The CEA Trial findings have been corroborated by the larger FACS trial. If the CEA trial results had been made available in 1994, and there is no evident reason why they should not have been, a more critical scrutiny of the evidence base that was used to bring liver and lung metastasectomy into practice. (25;30)~~(23;28)~~ might have been undertaken. The CEA Trial was a well-conceived and meticulously executed randomised trial and we hope that publishing it now more than twenty years after its completion will indicate the possibility of more randomised trials in surgery.(48)~~(46)~~

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Legends

Figure 1. The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.(1)~~(4)~~

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.(15)~~(12)~~

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.(1)~~(4)~~

Figure 4. Decision making algorithm for CEA to trigger second-look surgery.(15)~~(12)~~

Figure 5. Flow chart of enrolled and ultimately randomised patients. 'Blind' in the bottom left box means that the clinical teams were unaware of the elevated CEA discovered and were unaware that the patients have been randomised. They were indistinguishable amongst the 1230 non-randomised patients who were being followed-up. (See Figure 6)

Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from Office for National Statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230) Some would have had clinically evident early recurrence precluding randomisation. The initial plateau is an illustration of a death free interval(49)~~(47)~~ or "immortal time bias"(50)~~(48)~~ Patients in prospective studies may have a built in obligatory survival time from some starting point in order to attain the requirements to be included in the data set. This is an artefact but may be absorbed into survival time adding to and not readily distinguished from survival time attributed to treatment.

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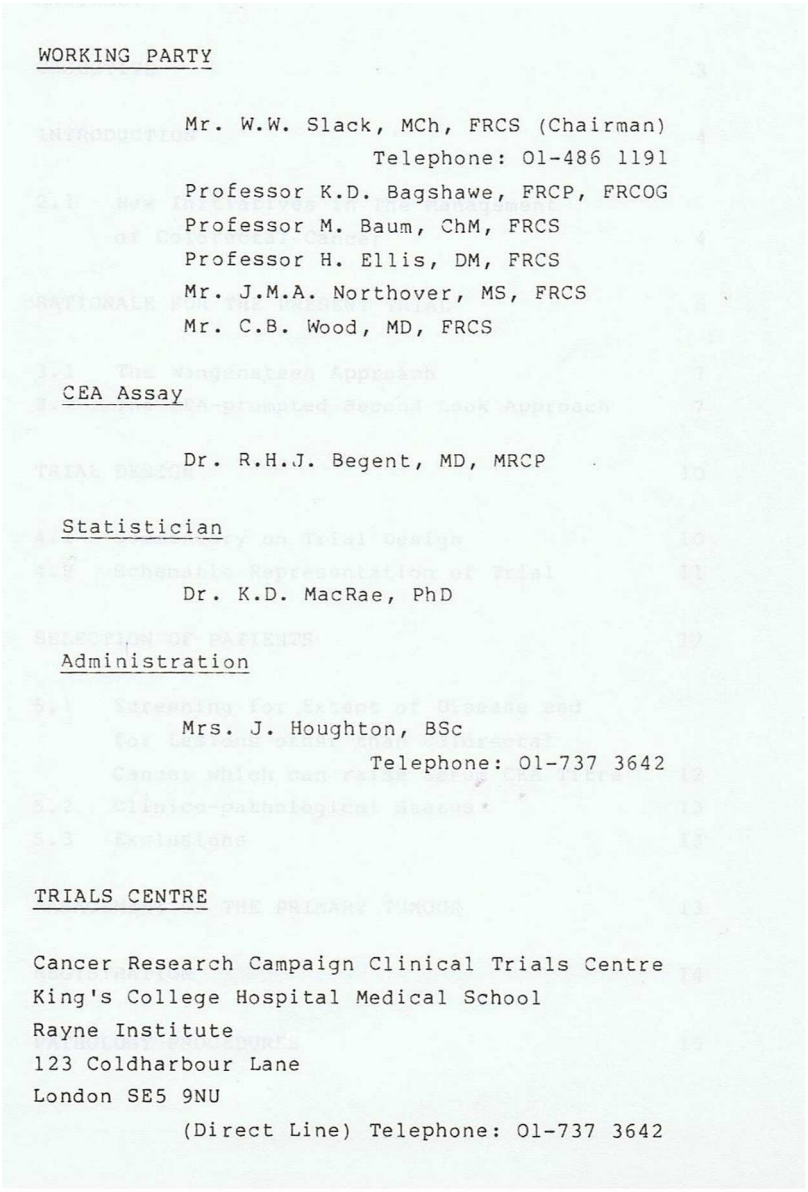

WORKING PARTY

Mr. W.W. Slack, MCh, FRCS (Chairman)
Telephone: 01-486 1191
Professor K.D. Bagshawe, FRCP, FRCOG
Professor M. Baum, ChM, FRCS
Professor H. Ellis, DM, FRCS
Mr. J.M.A. Northover, MS, FRCS
Mr. C.B. Wood, MD, FRCS

CEA Assay

Dr. R.H.J. Begent, MD, MRCP

Statistician

Dr. K.D. MacRae, PhD

Administration

Mrs. J. Houghton, BSc
Telephone: 01-737 3642

TRIALS CENTRE

Cancer Research Campaign Clinical Trials Centre
King's College Hospital Medical School
Rayne Institute
123 Coldharbour Lane
London SE5 9NU
(Direct Line) Telephone: 01-737 3642

The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.(4)
90x134mm (300 x 300 DPI)

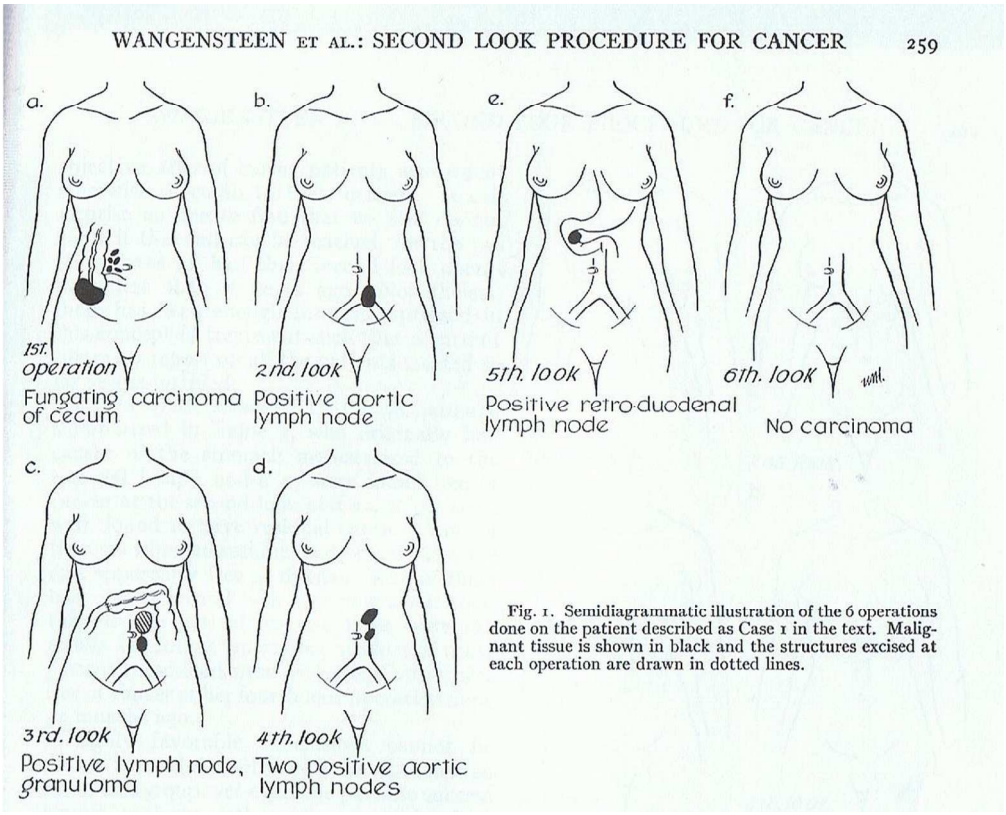

Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]
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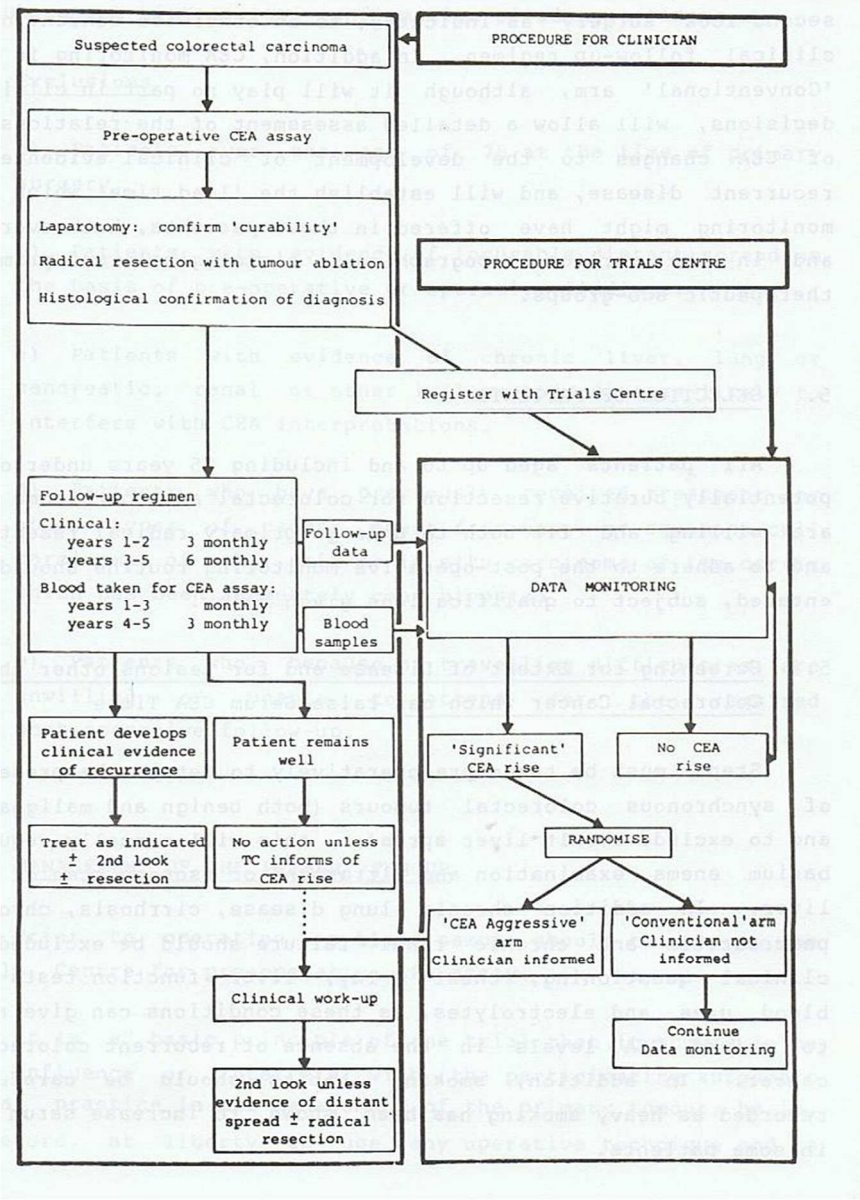

Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]
64x90mm (300 x 300 DPI)

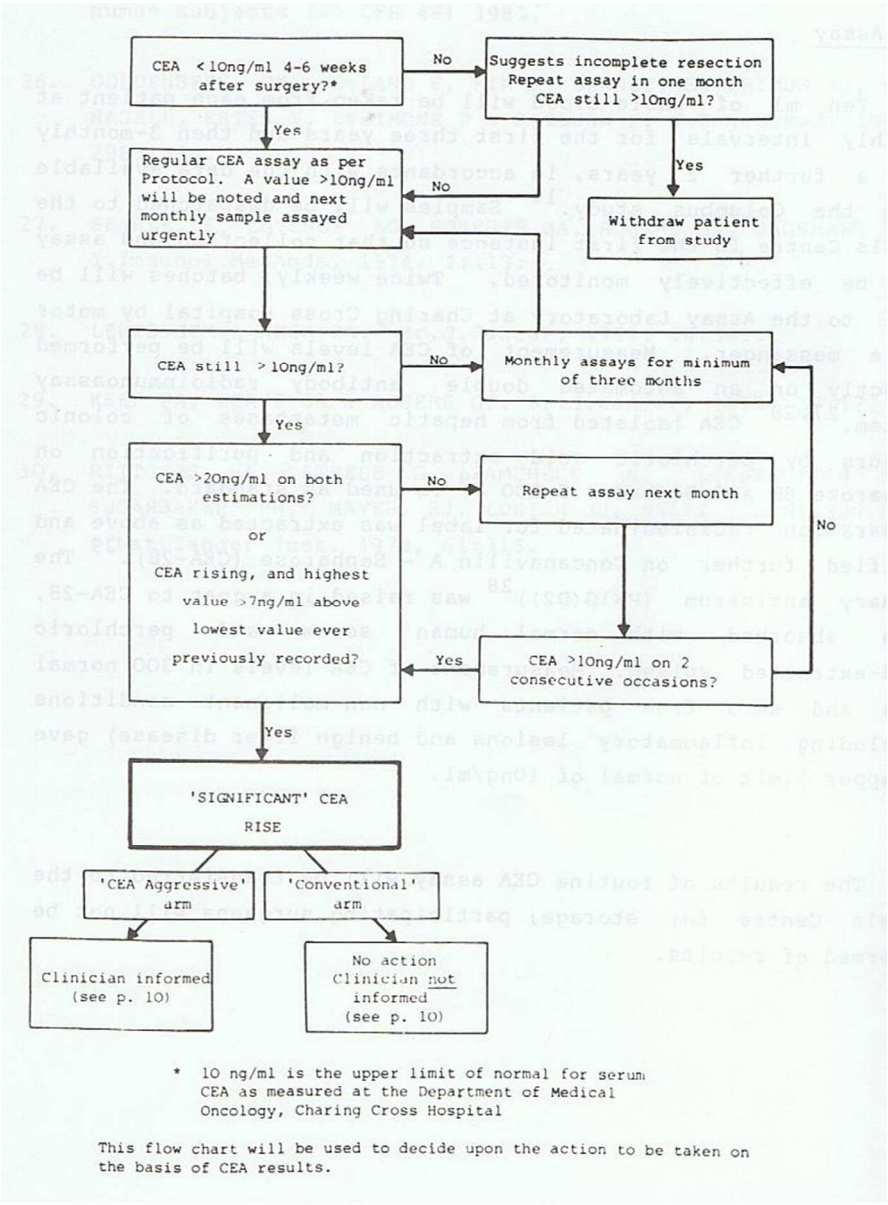

Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22]
66x90mm (300 x 300 DPI)

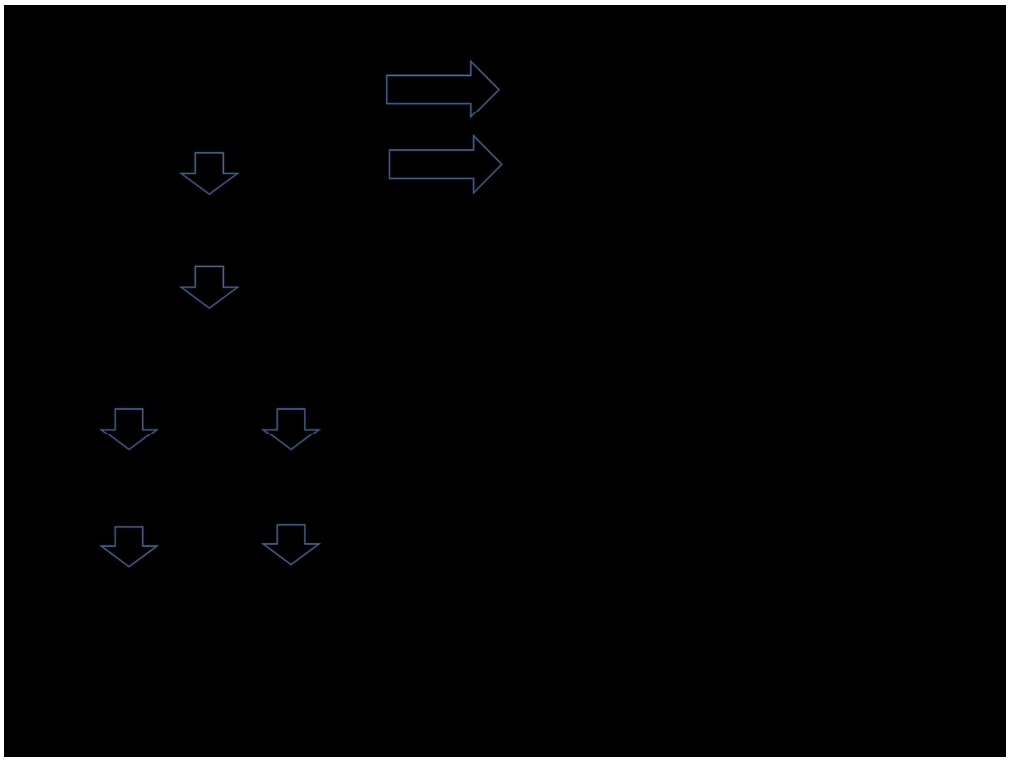

Figure 5. Flow chart of enrolled and ultimately randomised patients
119x90mm (300 x 300 DPI)

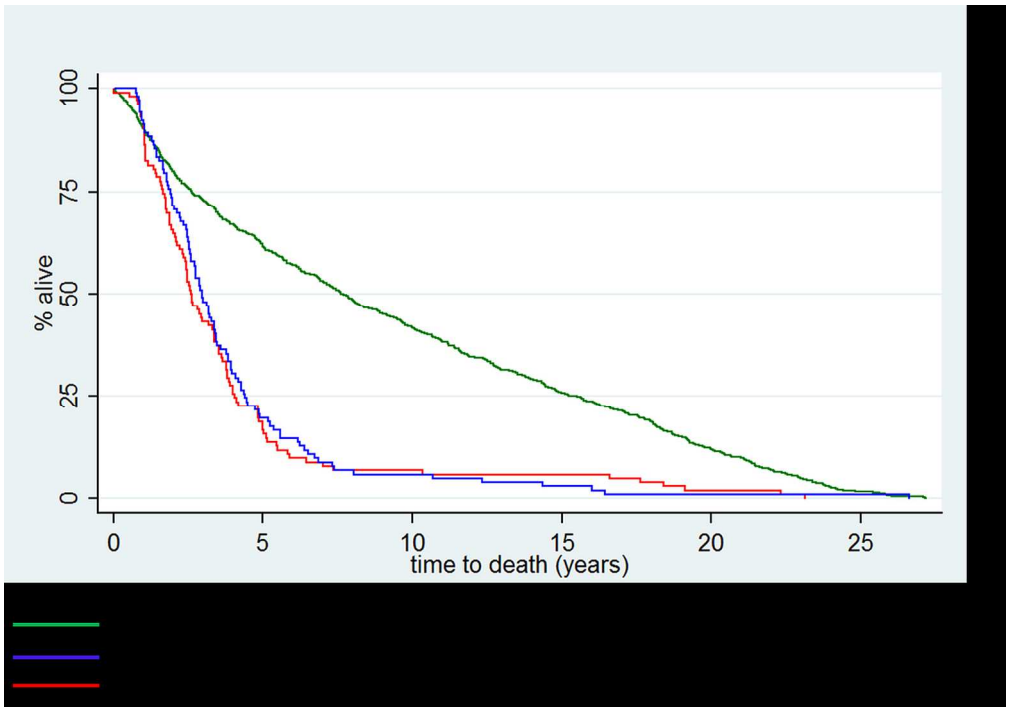

Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from ONS statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230) Some would have had clinically evident early recurrence precluding randomisation. The initial plateau is an illustration of a death free interval[44] or "immortal time bias"[45] Patients in prospective studies may have a built in obligatory survival time from some starting point in order to attain the requirements to be included in the data set. This is an artefact but may be absorbed into survival time adding to and not readily distinguished from survival time attributed to treatment.

RIAT Audit Record (RIATAR)

*A tool for documenting the transformation from regulatory documents to journal publication, based on the CONSORT 2010 checklist of information to include when reporting a randomised trial**

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
Title and abstract						
	1a	Identification as a randomised trial in the title	1	Cover	1	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3	1-2	None written	
Introduction						
Background and objectives	2a	Scientific background and explanation of rationale	5-6	4-9	None written	
	2b	Specific objectives or hypotheses	3	2	2	
Methods						
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7	10-11	2	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	None	None	None	
Participants	4a	Eligibility criteria for participants	7-8	12-13	2-3	
	4b	Settings and locations where the data were collected	12	Not stated	Not stated CEA assays 4	This was of course implicit that these were in units performing colorectal cancer

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
						surgery within hospitals
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10	16,18	4, 6-7	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed. NOTE “lead time” was a planned analysis There was also reference to “parallel studies”	7	2 21	7	I cannot see that this was explicitly stated in current terminology but it was all cause mortality and that is implicit throughout and not in doubt.
	6b	Any changes to trial outcomes after the trial commenced, with reasons	None	None	None	
Sample size	7a	How sample size was determined	10-11	19	7	Lacks clarity and 2000 suggests a degree of “ballpark” but it is there.
	7b	When applicable, explanation of any interim analyses and stopping guidelines	10-11	19	7-8	
Randomisation:						
Sequence generation	8a	Method used to generate the random allocation sequence	9		5	
	8b	Type of randomisation; details of any	9		5	This is not very

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
		restriction (such as blocking and block size)				detailed but is all we found.
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9-10		5-6	This was dealt with in some detail in the 1994 manuscript.
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10			Patients were enrolled by participating clinicians and it is quite clear that it was the trial centre that randomised.
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	10			
	11b	If relevant, description of the similarity of interventions				
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13			
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A			
Results						
Participant flow	13a	For each group, the numbers of	12-13		9	

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
(a diagram is strongly recommended)		participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome				
	13b	For each group, losses and exclusions after randomisation, together with reasons	13 Lines 506-10 are the restorative analysis		None recorded	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12		9	
	14b	Why the trial ended or was stopped	12		9	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13		17	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12 12 13		11	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Survival 13 Lead time 14		10 9	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended				
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory				

Section/Topic	Item No	Checklist item	Reported on page No of RIAT manuscript	Protocol from 1982 Pages numbered are as separate JPG files	Ms pdf 1994	Notes
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not dealt with			I don't think the data are good enough to document these and they are implicit in the stopping decision. They could be discussed if required.
Discussion						
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14			
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15			
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15			
Other information						
Registration	23	Registration number and name of trial registry				
Protocol	24	Where the full trial protocol can be accessed, if available	UCL			
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	None		CRC	

* The aim of this audit tool is provide a permanent record of the parts of text, tables and figures of the source Clinical Study Report (CSR) selected for inclusion into the RIAT manuscript submitted for publication. This tool is based upon checklist items described in the CONSORT 2010 statement, which is a widely adopted standard for reporting randomised trials. RIAT authors should consult the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. Similar audit records can be created for other types of trials by adapting other CONSORT extensions, e.g. for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. See www.consort-statement.org for more details.