



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

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Title

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

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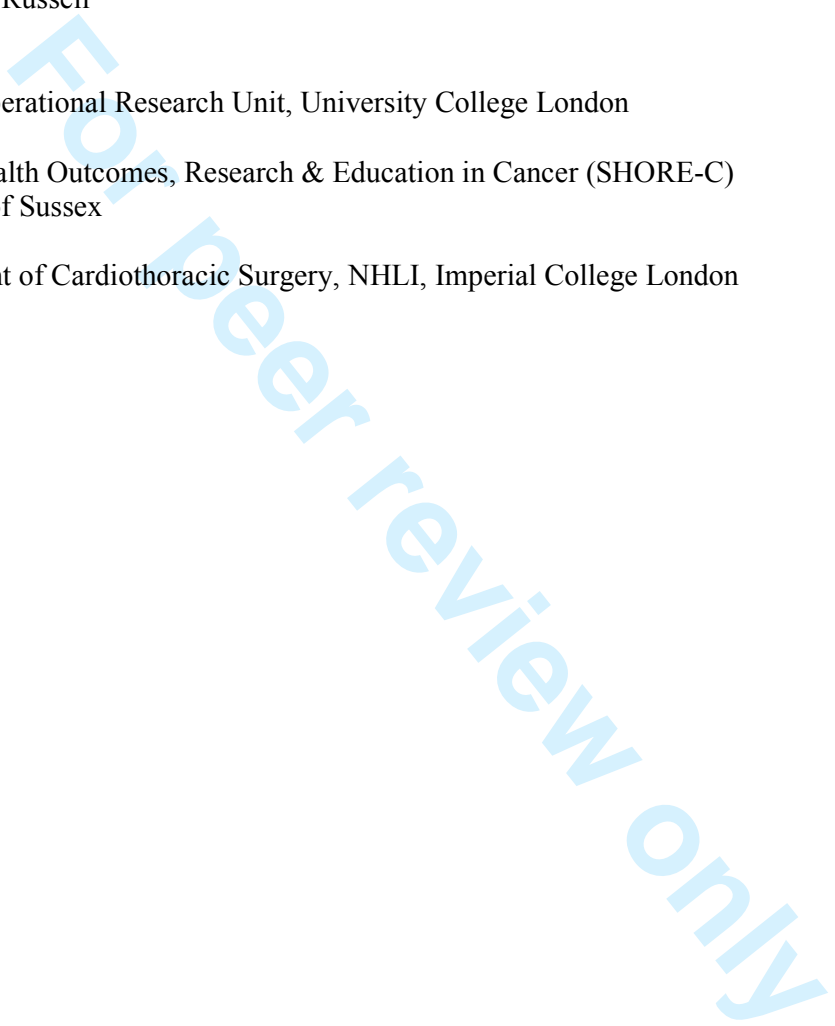
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4 22 Abstract

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6 23 Objectives: in patients who have undergone a potentially curative resection of colorectal  
7 24 cancer does a 'second-look' operation to resect recurrence, prompted by monthly  
8 25 monitoring of carcinoembryonic antigen, confer a survival benefit?

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10  
11 26 Design: randomised controlled trial

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13 27 Setting: 58 hospitals in the United Kingdom and Europe.

14  
15 28 Participants: from 1982 to 1993, 1447 patients were enrolled. After protocol exclusions  
16 29 1235 were eligible and of them 216 met the criteria for CEA elevation and were  
17 30 randomised to 'Aggressive' or 'Conventional' arms.

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19  
20 31 Interventions: 'second-look' surgery with intention to remove any recurrence discovered.

21  
22 32 Primary outcome measure: survival.

23  
24 33 Results: by February 1993, 88/108 patients had died in the 'Conventional' arm compared  
25 34 with 91/108 in the 'Aggressive arm'. The hazard ratio for Conventional to 'Aggressive'  
26 35 arms was 0.84 (95% confidence intervals 0.62-1.13; P=0.25). By 2011 a further 25  
27 36 randomised patients had died. Kaplan Meier showed no difference in long-term survival.

28  
29  
30 37 Conclusions: the trial was closed in 1993 following a recommendation from the Data  
31 38 Monitoring Committee that it was highly unlikely that any survival advantage would be  
32 39 demonstrated for CEA prompted second-look surgery. This conclusion was confirmed by  
33 40 repeat analysis after twenty years.

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3 43 Strengths and limitations of this study  
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- 5 44 • The CEA Second-Look Trial was a well planned and carefully executed study with a  
6 45 clear question and a well defined outcome of interest.
- 7  
8 46 • Second-look surgery prompted by the best available indicator of recurrence at the  
9 47 time conferred no survival advantage.
- 10  
11 48 • A further strength, and a reason to publish this trial now, is that it shows that  
12 49 randomised trials in surgery can be done and that the result may be counter the beliefs  
13 50 and expectations of practitioners based on their uncontrolled observations.
- 14  
15 51 • A limitation is that present day means of detection, based on imaging and anatomical  
16 52 localisation, may detect patients with recurrence curable by surgery. It follows that  
17 53 the effectiveness of second-look surgery prompted by new imaging methods cannot  
18 54 be assumed but should be the subject of controlled trials.

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## 56 Introduction

57  
58 It was observed during the 1970s that the outlook for patients with colorectal cancer was not  
59 as good as many had believed – only one in four patients survived for five years after  
60 diagnosis, while radical surgery, when feasible, was curative in under half of the patients [1]  
61 and results had not improved in several decades.[2-4] Attempts to improve prognosis by  
62 refinements in primary operative techniques had not made a difference[5] and it was  
63 considered unlikely that technical modifications would lead to improvement in survival  
64 following surgery.[1;2] The objective of the CEA Second-Look Surgery Trial was to  
65 determine whether, following potentially curative primary surgery for colorectal cancer, the  
66 mortality could be decreased by a policy of second-look surgery prompted by rising serum  
67 carcinoembryonic antigen (CEA). The trial ran from 1982 to 1993. That there was no survival  
68 advantage was reported in 1994 to the British Oncological Association[6] and was published  
69 in a letter to the Journal of the American Medical Association.[7]  
70

71 Surgery for colorectal cancer recurrence has since become routine both in the form of hepatic  
72 resection[8] and pulmonary metastasectomy[9] but without evidence from controlled trials  
73 for either practice.[10] When doubts were raised about the security of the evidence in the  
74 British Medical Journal in 2007[11] a general belief existed that randomised controlled trials  
75 of the effectiveness of resection of liver or lung metastases were not possible and were not  
76 needed. These paired beliefs are brought into question by the CEA Second-Look Trial: the  
77 presumed benefit of surgery of recurrence was not seen when subjected to a randomised  
78 controlled trial.[6;7]  
79

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

81 The RIAT restorative authors had been involved in various studies related to surgery for  
82 disseminated colorectal cancer[11-13] including a conundrum as to whether discovery of an  
83 elevated CEA assay should prompt or be considered a contra-indication to pulmonary  
84 metastasectomy.[14] We knew the CEA trial to have been enrolling patients in the 1980s but  
85 when we searched the literature for the result of the trial we learned that it had been  
86 abandoned in 1994. In 2009 we contacted the chief investigator of the trial and the present  
87 director of the unit. The data were initially thought to be irretrievably lost or irrecoverable.  
88 However, staff at the trials centre retrieved archived CEA electronic files and the death data  
89 were updated. We gained access to anonymised electronic data in 2011. The process of data  
90 restoration is described later.  
91

92 Amongst the documents were listed the members of the trial development group in the 1982  
93 protocol[4] and the contributors to the 1994 manuscript.[15] None of these individuals  
94 expressed an interest in resuming work on the trial or were in a position to do so. When we  
95 contacted them later to share the restored data with them no one raised any objection but on  
96 the contrary encouraged us to publish our findings.  
97

### 98 Figure 1 Working Party from the 1982 Protocol

#### 100 Improving detection and treatment of recurrent disease: the context in 1982

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

106

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 3<sup>rd</sup> 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]

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3 154 **Methods: trial intent and design**

4 155 The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years  
5 156 and to follow them for five years. The study was specifically designed with late  
6 157 randomisation in order to maximise statistical power. It was originally intended to recruit  
7 158 2,000 patients with the anticipation that about 25% would show a CEA rise as the first  
8 159 evidence of possible recurrence. This number would have provided 90% power to detect an  
9 160 improvement in two year survival from the second-look procedure from 25% to 55% at  
10 161  $\alpha=0.05$ . The protocol stated that for the trial to be stopped prematurely very stringent levels  
11 162 of significance ( $p<0.001$ ) would be used.

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14 163  
15 164 After potentially curative surgery for colorectal cancer, all eligible patients were to be  
16 165 monitored identically using conventional clinical follow-up together with regular CEA assay,  
17 166 performed centrally. Clinicians would not be informed of the result. When a 'significant'  
18 167 CEA rise was recorded, patients were to be randomised by the Trials Centre into either  
19 168 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm, the  
20 169 clinician would immediately be informed of the CEA rise so that the patient could be  
21 170 urgently screened to exclude widespread metastatic disease or a non-malignant cause for the  
22 171 CEA rise. If neither was found, and the patient was medically fit for operation, second-look  
23 172 surgery to locate and remove any treatable recurrence was mandatory. In the case of patients  
24 173 in the 'Conventional' arm, the clinician would not be informed of the 'significant' CEA rise  
25 174 nor of subsequent randomisation to not have the CEA rise revealed.

26 175  
27 176 The CEA trial design was devised so that clinical follow-up would remain unbiased, and  
28 177 allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent  
29 178 colorectal cancer. The primary outcome was survival based on death certification through the  
30 179 Office of Population Censuses and Surveys (OPCS) (now called the Office of National  
31 180 Statistics (ONS)). No subset analyses were planned.

32 181  
33 182 The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical  
34 183 Trials Centre at King's College Hospital. CEA assays were performed using a  
35 184 radioimmunoassay technique at a single centre at Charing Cross Hospital.

36 185  
37 186 The intention as stated in the protocol was that the trial would produce:

- 38 187  
39 188 a) a definitive answer concerning the effectiveness of CEA-prompted second-look  
40 189 surgery to improve survival  
41 190 b) an accurate picture of the 'lead time' produced by CEA compared to clinically  
42 191 indicated second-look surgery  
43 192 c) further data relating CEA levels to tumour histology and topography, and  
44 193 d) a large data base on the natural history of colorectal cancer.[4]

45 194  
46 195 The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements  
47 196 give no indication as to the precise nature of analyses that might follow and are regarded as  
48 197 opportunities for explanatory subset analyses which were not in the event carried out.

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51 200 **Methods: the conduct of the trial 1982 to 1993**

52 201 *Selection of patients*

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3 202 All patients up to the age of 76 who had undergone a potentially curative resection for  
4 203 adenocarcinoma of the colon or rectum, who were fit and willing to adhere to the post-  
5 204 operative monitoring routine were eligible for the study. After the patient had given informed  
6 205 consent, the surgeon was required to take any action considered necessary to detect the  
7 206 presence of synchronous colorectal tumours (both benign and malignant) and to exclude  
8 207 occult liver spread; usually by performing barium enema examination and ultrasound or CT  
9 208 scan of the liver. In addition, chronic lung disease, cirrhosis, chronic pancreatitis, and  
10 209 chronic renal failure, all of which can give raised CEA levels in the absence of recurrent  
11 210 colorectal cancer were excluded by clinical questioning, chest x-ray, liver function tests,  
12 211 blood urea and electrolytes. Smoking habits and alcohol consumption were recorded as  
13 212 heavy smoking or drinking, or a change in these habits, can influence CEA levels.  
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16 213  
17 214 Patients were excluded if there was evidence of incurable distant spread, either pre-  
18 215 operatively or during the primary operation, or if the CEA level failed to return to the normal  
19 216 range (<10 ng/ml) within six weeks of primary surgery. Patients who had previously  
20 217 received treatment for other types of cancer, apart from basal or squamous cell carcinoma of  
21 218 the skin or in-situ carcinoma of the cervix adequately cone biopsied, were excluded from the  
22 219 study.  
23

#### 24 221 *Management of the primary tumour*

25 222 It was a basic principle that the trial should in no way influence or interfere with the  
26 223 participating surgeon's practise and management of the primary disease. The surgeon was,  
27 224 therefore, at liberty to use any operative technique and to employ peri-, or post-operative  
28 225 radiotherapy, or adjuvant chemotherapy as was seen fit. All that was asked of the surgeon  
29 226 was that to remain consistent as to the treatment used for any particular type of disease.  
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#### 32 228 *Patient Entry*

33 229 A pre-operative blood sample for CEA assay was taken from all patients with suspected  
34 230 colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. Entry to the trial  
35 231 required potentially curative resection of the primary tumour. If at laparotomy, a potentially  
36 232 curative resection was performed and subsequent histology confirmed the diagnosis of  
37 233 adenocarcinoma, the patient was given a full explanation of the study and could be registered.  
38  
39

40 235 Figure 3: Trial flow diagram  
41 236

#### 42 237 *Monitoring of Patients*

43 238 Clinical follow-up of all patients continued in an identical manner (three monthly for the first  
44 239 two years and six monthly for the next three years) whilst blood for CEA assay was drawn  
45 240 monthly for the first three years and three monthly for the next two years. If the patient  
46 241 remained well and the CEA was within normal limits as defined by a pre-tested algorithm the  
47 242 monitoring continued according to the schedule.  
48  
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#### 50 244 *CEA assay*

51 245 Ten mls of whole blood were taken from each patient at monthly intervals for the first three  
52 246 years and at three monthly intervals for the next two. The serum was separated and sent to  
53 247 the Trials Centre in special plastic phials. Having logged the receipt of the sample, the trial's  
54 248 secretariat forwarded them in batches, two or three times weekly, to the Medical Oncology  
55 249 Department at Charing Cross Hospital for assay. The results were returned to the Trials  
56 250 Centre for recording and action if appropriate. This centralised system was to ensure that all  
57 251 participating clinicians were kept blind as to the CEA results for all trial patients. It also  
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252 ensured quality control of the CEA assay as there was no possibility of inter-laboratory  
253 variation.

254  
255 Serum CEA values were measured by double antibody radioimmunoassay.[31-33] A bank of  
256 serum samples has been retained at -20°C.

257  
258 Throughout the trial the compliance with the regular blood sampling was monitored by the  
259 secretariat. Clinicians were reminded each month of the patients for whom samples were  
260 due; those who had missed the previous visit were highlighted as urgent. The percentage  
261 compliance for each participating patient was calculated as the number of samples received  
262 divided by those expected (12 or 13 per year depending on whether the phlebotomy was  
263 being done at 4 weekly or monthly visits) x 100. The median time between samples was also  
264 calculated. Failure to achieve 50% or less of the expected samples has been defined as poor  
265 compliance; the sensitivity to detect CEA rises in this group was greatly reduced and such  
266 patients were excluded from randomisation.

267  
268 The objective of the trial was to compare conventional care in the UK during the period of  
269 the trial and an identical policy but with the addition of CEA monitoring and second-look  
270 laparotomy for the management of any recurrent disease detected.

271  
272 Clinicians managing patients under the 'Conventional' policy were totally blind to the results  
273 of individual CEA assays. In designing the study, there was an inevitable compromise  
274 between employing CEA to its maximum advantage, by requesting an immediate repeat  
275 sample from any patient demonstrating a rise, and the essential blinding component, which  
276 did not allow for the request of additional samples. The design allowed only routine  
277 monitoring of CEA thus keeping all clinicians blind until after the randomisation for  
278 'Aggressive' arm patients and completely for all others.

279  
280 ***'Significant' Rises in CEA***

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

288  
289 Figure 4: CEA algorithm

290  
291 ***Randomisation***

292 For a patient to be randomised, compliance with the blood monitoring regimen had to be  
293 greater than 50% over the preceding nine months. Patients whose compliance was between  
294 50 and 70% or whose immediate post-operative sample had not been received within the 4 to  
295 6 week guideline were randomised in a separate stratum. Randomisation was also stratified  
296 by participating clinician. A block size of two was used in order to maintain as close a  
297 balance as possible between the two treatment arms. Clinicians were not only totally blind to  
298 half the randomisations (i.e. those in the 'Conventional' arm) but also to the assay values and  
299 hence the prospect of randomisation, prediction of the following allocation was not possible.

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3 301 If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise  
4 302 immediately by telephone from the trial centre and subsequently in writing and was requested  
5 303 to contact the patient urgently, and with the patient's permission, carry out a full clinical  
6 304 work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g., change in  
7 305 smoking or drinking habit) and also to identify if present, distant incurable spread. In the  
8 306 absence of these conditions the surgeon was requested to undertake a mini-laparotomy  
9 307 proceeding to a full laparotomy with macroscopic clearance of disease should this be  
10 308 possible. Prior to surgery patients were made fully aware of the situation including the fact  
11 309 that they had been randomised within the trial to undergo a second-look procedure. This was  
12 310 only undertaken if the patient gave informed consent.  
13 311

14 312 For patients randomised to the 'Conventional' arm no further action was taken; the clinician  
15 313 was not informed that the CEA had risen nor that the patient had been randomised.  
16 314

17 315 If at any stage a patient in the study developed clinical evidence of recurrent disease the  
18 316 clinician was at liberty to manage the patient according to usual practice. If the disease was  
19 317 in the abdomen and was thought to be treatable by a second-look operation with re-resection,  
20 318 this was perfectly acceptable. The clinician was blind as to whether such patients had been  
21 319 randomised to the 'Conventional' arm of the trial or had not been randomised because the  
22 320 CEA had failed to denote the presence of recurrent disease.  
23 321

### 24 322 *Second-Look Laparotomy*

25 323 The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate  
26 324 any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was  
27 325 detected all that was required prior to closure, was biopsy. Otherwise following a full  
28 326 excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the  
29 327 small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis  
30 328 was undertaken. The liver was fully mobilised to determine whether any tumour was present.  
31 329 Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then  
32 330 carried out with the objective of total extirpation of all recurrence. Complete data recording  
33 331 of the procedure along with the results of the histology of all potentially involved sites was  
34 332 required by the trial's office.  
35 333

36 334 For patients in whom a radical resection was achieved after second-look surgery (motivated  
37 335 either on clinical information or because the patient had been randomised to the 'Aggressive'  
38 336 arm) the follow-up schedules for clinical examination and blood sampling reverted to those  
39 337 following the primary operation. However, for the randomised patients, the 'Aggressive'  
40 338 policy was maintained in that clinicians were immediately notified of any CEA levels above  
41 339 10ng/ml.  
42 340

### 43 341 *Death*

44 342 Every patient registered onto the study was 'flagged' with the Office of Population Censuses  
45 343 and Surveys (OPCS) who provide automatic notification of date of death allowed the trial  
46 344 centre to receive minimum information on death for all patients.  
47 345

### 48 346 *Statistical Analysis*

49 347 The study was specifically designed with late randomisation in order to maximise statistical  
50 348 power. It was originally intended to recruit 2,000 patients with the anticipation that about  
51 349 25% would show a CEA rise as the first evidence of possible recurrence. This number would  
52 350 have provided 90% power to detect an improvement in two year survival from the second-  
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3 351 look procedure of 55% (i.e. from 25% to 55%) at  $\alpha=0.05$ . The protocol stated that for the  
4 352 trial to be stopped prematurely very stringent levels of significance ( $p<0.001$ ) would be used.  
5 353

6 354 A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not  
7 355 entering patients into the trial was asked to review the data after the first 100 patients had  
8 356 been randomised, which occurred in January 1988, and again after 200 patients had been  
9 357 randomised in February 1993, at which point it was recommended that the trial was stopped  
10 358 since it was very unlikely that any clinically important advantage would be demonstrated for  
11 359 patients undergoing second-look surgery.  
12 360

## 14 361 Methods of the RIAT process

### 15 362 *The data*

16 363 The RIAT restorative authors had been warned by the statisticians called in to look at the data  
17 364 in 2003-4 that “the databases were corrupted with key variables no longer abstractable” and  
18 365 that they could not be analysed without a lot of work.[34;35] We found that the data on  
19 366 paper and on file was accessible and we had no reason to doubt the veracity of individual  
20 367 items. The problem we found was that the electronic files had numerous problems with  
21 368 format which made the files on the 1447 individual patients difficult to handle but that the  
22 369 data entries were not themselves corrupted.  
23 370

24 371 One of the RIAT restorative authors (KM) had worked in the trials unit(s) during the time the  
25 372 CEA Trial data were being accrued and knew the systems in use and their changes but was  
26 373 not directly involved in this trial at any stage.  
27 374

28 375 The data problems encountered and resolved were as follows:  
29 376

- 30 377 • The codes that indicated that a patient had met the criteria for CEA elevation and then  
31 378 whether randomly allocated to ‘active’ or ‘Conventional’ were preserved and tallied  
32 379 with the number in the 1994 manuscript.[15]  
33 380
- 34 381 • There were variations in the way dates were recorded in the database. There had been  
35 382 migrations of data from a Prime server using ‘Universe’ to Excel and the  
36 383 interpretation of the present authors, with information from contemporary witnesses  
37 384 was that in undertaking the task operators did not always correctly specify these data  
38 385 as ‘dates’ when importing, and/or allowed them to be converted to American date  
39 386 formats. These errors prevented calculations and would have defeated running a  
40 387 survival analysis without correction. The dates were however visually readable and  
41 388 not ‘corrupt’. Some could be corrected by running current versions of software.  
42 389 Others were manually corrected by re-entering them in a Microsoft date format.  
43 390 Paper records were available to resolve uncertainties.  
44 391
- 45 392 • The next problem was in linking these three groups of patients (randomised to  
46 393 ‘aggressive’, randomised to ‘Conventional’ and not randomised) to the dates for  
47 394 survival analysis. Individual patients were uniquely identified in the files by seven  
48 395 digit strings. To these had been added letters at the beginning and end of the strings  
49 396 flagging them for trial administrators’ checklists and perhaps for subgroup analysis.  
50 397 Once the problem was identified, and we had established that the initial and terminal  
51 398 letters were redundant for analysis of the primary endpoint, it was a straightforward  
52 399 matter, in expert hands, to write code to restore the seven digit strings.  
53 400

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2  
3 401 • It was evident that the seven digits did not represent a simple sequence but certain  
4 402 positions identified particular centres. We then recognised a consistent pattern of  
5 403 mismatch. The fourth digit differed systematically so what was a zero in one file was  
6 404 an 8 in the other with all other digits remaining the same. It was suggested to us that  
7 405 the fourth digit replacement was used to identify patients suitable for *post hoc*  
8 406 subgroup analyses but no documentation was found to confirm this. By checking  
9 407 back to the dates of birth we were able to confirm that this systematic correction  
10 408 resolved the problem and most of the data were then usable.  
11 409
- 12  
13 410 • By ranking all the data in the paired files for line by line visual inspection residual  
14 411 discrepancies were identified. Scrutinising the digit strings allowed for seven of the  
15 412 remaining eight pairs to be reconciled and verified on dates of birth. We failed to  
16 413 resolve only one out of 1447 records in each file.  
17 414
- 18  
19 415 • Inspection of the accrual of death dates was discontinuous for a couple of years  
20 416 suggesting a lapse in either recovery or entry. The current trials centre obtained  
21 417 permission to re-run the Office of National Statistics (ONS) search in July 2012.  
22 418

23 419 It should be remembered that the data collection ran from 1982 to 1993 during which time  
24 420 there was a multiplicity of operating systems, disc drives and software. Nevertheless we had  
25 421 electronic files in Microsoft excel spread sheets in recognisable formats. We identified  
26 422 several problems but they were systematic and not random (we would not use the value laden  
27 423 word 'corrupted'). We were able to rectify the formatting errors and verify that the data used  
28 424 for our analysis were correct. The Kaplan Meier analysis was re-run.  
29 425

## 30 426 31 427 32 428 **Results**

33 429 The study opened to recruitment in November 1982 and was closed by the Working Party, on  
34 430 the acceptance of a recommendation from the Data Monitoring Sub-committee, on 17th  
35 431 February 1993. During this period 1,447 patients were registered by 73 participating  
36 432 clinicians in 58 hospitals in the United Kingdom and Europe. Of these 39 (2.7%) were  
37 433 deemed ineligible since their CEA did not fall below 10 ng/ml by six weeks after surgery. A  
38 434 further 173 patients were excluded from analysis; four did not have a confirmed diagnosis of  
39 435 adenocarcinoma, 6 were considered unfit for continued monitoring, 4 had a previous and 1 a  
40 436 simultaneous non-colorectal malignancy, 2 had metastatic disease, and 156 (10.8%) although  
41 437 apparently willing never complied with the requirement for monthly blood sampling or only  
42 438 did so for 3 months or less.

## 43 439 **Figure 5**

44 440 In the 1,235 patients who continued in the trial, 80% achieved a greater than 60% compliance  
45 441 with blood sampling; whilst 12.5% registered between 40-59% of the required samples and  
46 442 only 7.5% had compliance of less than 40%. The majority of randomisations (160/216; 74%)  
47 443 were prior to the second anniversary of the primary diagnosis. Three patients randomised  
48 444 had prior recurrent (2) or metachronous (1) disease detected clinically, without a rise in CEA  
49 445 and were operated upon.  
50 446

51 447 Two hundred and sixteen patients developed a 'significant' rise in CEA and as no recurrent  
52 448 disease had been recorded at their latest trial follow-up, they were randomised by the Trial  
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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 <sup>1</sup>	36 (33.3)	38 (35.2)
Dukes' C <sup>2</sup>	17 (15.7)	10 ( 9.3)
Missing	4 ( 3.7)	6 ( 5.6)

456

457

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%.

460

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.

470

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.

474

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.

479

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.

485

Figure 6 Kaplan Meier analysis

487



1  
2  
3 488 The lead time conferred by CEA monitoring, defined as the median time to clinically  
4 489 detected disease for patients randomised to the 'Conventional' arm, was 323 days (SE 60;  
5 490 95% confidence interval (CI) 203-443). This is expressed visually (Figure 6) as an analysis  
6 491 of time to confirmed recurrent disease in the randomised patients according to their  
7 492 therapeutic arm. This analysis included censored observations on 23 patients, however only  
8 493 five of these had a censored time less than the lead time. It was regarded as unlikely,  
9 494 therefore, that the lead time would decrease as further events occur. The analysis presented to  
10 495 the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA  
11 496 versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs  
12 497 70% at a year.

13 498  
14 499 Figure 7 Lead time.

## 15 500 16 501 Discussion

17 502 We have restored data sufficient to achieve the primary outcome of interest as specified by  
18 503 the CEA trialists:

19 504 “Does a policy of CEA-prompted second-look surgery following ‘curative’ resection  
20 505 of colorectal cancer produce a decrease in morbidity and mortality due to tumour  
21 506 recurrence, despite sequelae of second look surgery?”  
22 507

23 508 The answer is that detecting and acting on CEA elevation did not reduce mortality. That  
24 509 finding led to the closing of the trial in 1994[6;7] and we confirm it here. There was small  
25 510 non-significant excess of deaths in the ‘Aggressive’ arm. The burden of morbidity  
26 511 attributable to the greater number of investigations and operations was not captured by the  
27 512 trial protocol.  
28 513

29 514 The second planned analysis was to obtain an accurate picture of the ‘lead time’ produced by  
30 515 CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up  
31 516 patients considerably sooner than the clinical methods available at the time by about six  
32 517 months to a year.  
33 518

34 519 Use of CEA is currently used by some for this purpose but in development of the PulMiCC  
35 520 trial we found variability in its use and inconsistency in the threshold used.[14] Other  
36 521 methods of investigation (MRI, PET and improved CT and echo) are now used to detect  
37 522 recurrence before it is clinically evident. It cannot be presumed, and on the basis of the CEA  
38 523 Second-Look Trial results there is doubt, as to whether earlier detection leading to further  
39 524 surgery, leads to better outcomes.  
40 525

41 526 The third and fourth intentions set out by the CEA trialists were c)to obtain further data  
42 527 relating CEA levels to tumour histology and topography and d) a large data base on the  
43 528 natural history of colorectal cancer.  
44 529

45 530 Multiple CEA assay results exist in the data we hold for 1446 patients which could now be  
46 531 linked to survival as a result of the RIAT restorative work. The opportunity for further  
47 532 analysis exists and an approach for access to these data been received.  
48 533

49 534 With respect to the natural history of colorectal cancer although we trust the death  
50 535 certification data for the date of death it has been shown that “at least a third of all death  
51 536 certificates are likely to be incorrect”[36]. No doubt aware of this and seeking much more  
52 537 detailed information, the CEA Trialists asked for detailed post-mortem examinations many of  
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3 538 which are in the trial documents. Given the many differences in cancer evaluation and  
4 539 imaging in the intervening thirty years we would be cautious about their value now.  
5 540 Furthermore it appears that it was disagreement concerning explanatory analyses which  
6 541 contributed to failure to publishing the primary outcome of interest.[15] The purpose of such  
7 542 analyses is to discover subsets of patients in whom there was a benefit from the intervention  
8 543 under evaluation and to thus determine the characteristics of patients in whom the  
9 544 intervention might have had a beneficial effect by analysis of mediators and moderators.[37]  
10 545 There is a general objection to this exercise because it can lead to spurious  
11 546 associations.[38;39] Furthermore when there is no overall benefit found, as in the CEA  
12 547 Second-Look Trial, any subgroup(s) where there is a positive association between  
13 548 intervention and outcome, must be balanced by one or more other groups where there was net  
14 549 harm. There were no completed subset analyses in 1994 and we have not attempted any in  
15 550 restoring the trial.

16  
17  
18 551  
19 552 The answer to the primary research question was clear in 1993 and was the explicit reason for  
20 553 stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery  
21 554 had been missed and in the absence of benefit there was net harm being done to the patients.  
22 555 We cannot say whether this is an inevitability associated with any form of second-look  
23 556 surgery for colorectal cancer and that these findings of the CEA Trials will apply to any other  
24 557 means of selecting patients for second-look surgery. The forms of second look surgery now  
25 558 widely practiced in colorectal cancer are liver and lung resection of metastases.

26 559  
27  
28 560

- Full mobilisation of the liver at second-look laparotomy was included in the CEA  
29 561 Trial protocol. Hepatic resection has entered routine practice based on observational  
30 562 data[40] and an opportunity to do a randomised trial, for which a power calculation  
31 563 was proposed in 1992 from the Mayo Clinic[41] was not taken.[8]
- Two patients had a thoracotomy prompted by CEA elevation. Pulmonary  
32 564 metastasectomy for colorectal cancer is, after primary lung cancer, the second  
33 565 commonest thoracic cancer operation and is the subject of an ongoing randomised  
34 566 controlled trial.[42]

35 567  
36 568  
37 569 If the CEA Trial findings result can be generalised, and there is no obvious reason in  
38 570 principle why they should not be, it would suggest that more critical scrutiny of the evidence  
39 571 base used to bring surgery into practice is justified. The CEA Trial was a well conceived and  
40 572 meticulously executed randomised trial and we hope that publishing it now more than twenty  
41 573 years after its completion will indicate the possibility of more randomised trials in  
42 574 surgery.[43]



1  
2  
3 575 Legends

4 576

5 577 Figure 1. The “Working Party” that produced the protocol in 1982 for the CEA Second-Look  
6 578 Surgery trial.[4]

7 579

8 580 Figure 2. Illustration of operative findings in six successive operations seeking recurrence of  
9 581 colorectal cancer.[22]

10 582

11 583 Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]

12 584

13 585 Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22]

14 586

15 587 Figure 5. Flow chart of enrolled and ultimately randomised patients

16 588

17 589 Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446)  
18 590 following potentially curative colorectal cancer surgery. Patients who had CEA elevation  
19 591 according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA  
20 592 revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from ONS  
21 593 statistics in 104/108 in each arm. The green line is for all other patients. (N=862 of 1230)  
22 594 Some would have had clinically evident early recurrence precluding randomisation. The  
23 595 initial plateau is an illustration of a death free interval[44] or “immortal time bias”[45]  
24 596 Patients in prospective studies may have a built in obligatory survival time from some  
25 597 starting point in order to attain the requirements to be included in the data set. This is an  
26 598 artefact but may be absorbed into survival time adding to and not readily distinguished from  
27 599 survival time attributed to treatment.

30 600

31 601 Figure 7. Illustration kindly provided by JMAN which was as used by him in presentations  
32 602 related to the analysis of the DMC in 1993. We have not verified the dates of detection but  
33 603 there is no reason to doubt them and it remains a valid illustration of the efficacy of CEA  
34 604 monitoring I detecting recurrence but does not alter the conclusion that second-look surgery  
35 605 prompted by it is ineffective in improving survival.

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#### 30 644 Contributor statement

31 645 TT instigated the recovery of the data, worked on the database recovery described in the  
32 646 manuscript and wrote the first and edited the final version of the manuscript.  
33 647 KM navigated the data files and worked on the database recovery described in the  
34 648 manuscript.  
35 649 FF performed the analysis of the recovered data and the presentation of the analysis.  
36 650 RCGR negotiated access to the data and with TT contacted and interviewed the members of  
37 651 the original trial team.  
38 652 All authors have read and contributed to successive iterations of the manuscript and approve  
39 653 the submitted version.  
40  
41 654

#### 42 655 Data sharing

43 656 We are prepared to share the data in our possession and to direct any applicants for stored  
44 657 data to the head of the trial centre where the data are still held.  
45  
46 658

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48 660 We have agreed with the CEA Trialists that the RIAT restorative authors intend to fully  
49 661 acknowledged them (which they all welcomed) but that their individual inclusion and its  
50 662 wording could await a better idea of where and how this will appear. No members of the  
51 663 present Trial Centre (as we understand it) had any involvement with the CEA trial and while  
52 664 we will wish to acknowledge access to data we are not yet sure exactly what form this will  
53 665 take.  
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Figure 1. The "Working Party" that produced the protocol in 1982 for the CEA Second-Look Surgery trial.[4]  
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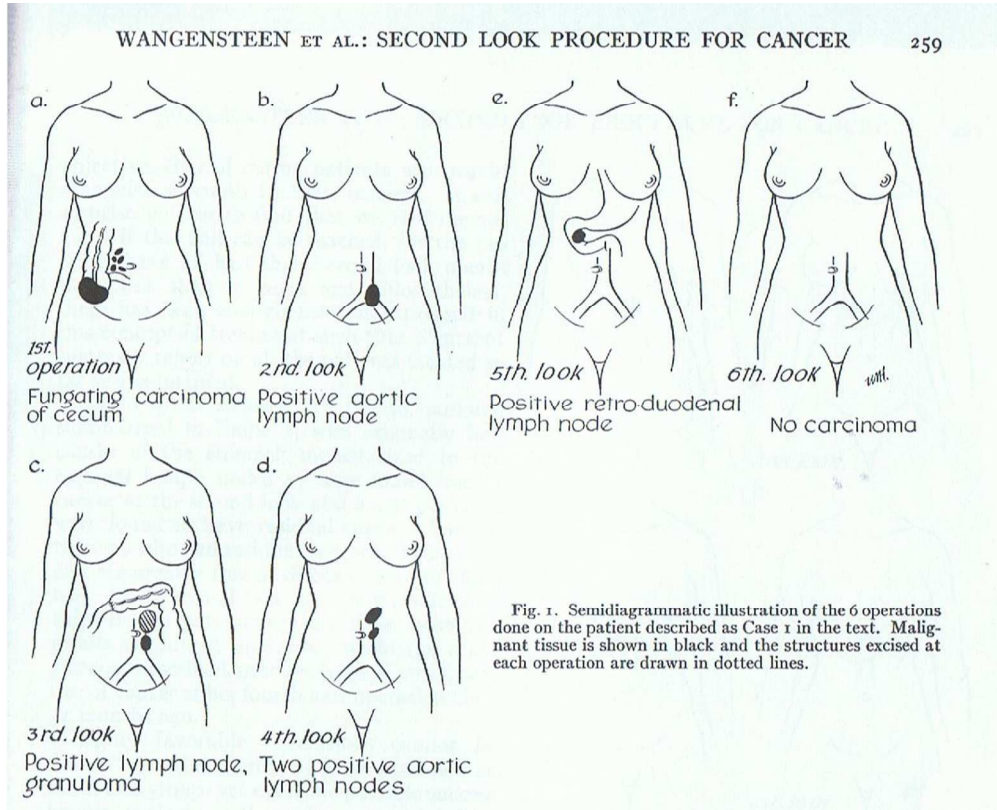


Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]  
161x130mm (200 x 200 DPI)



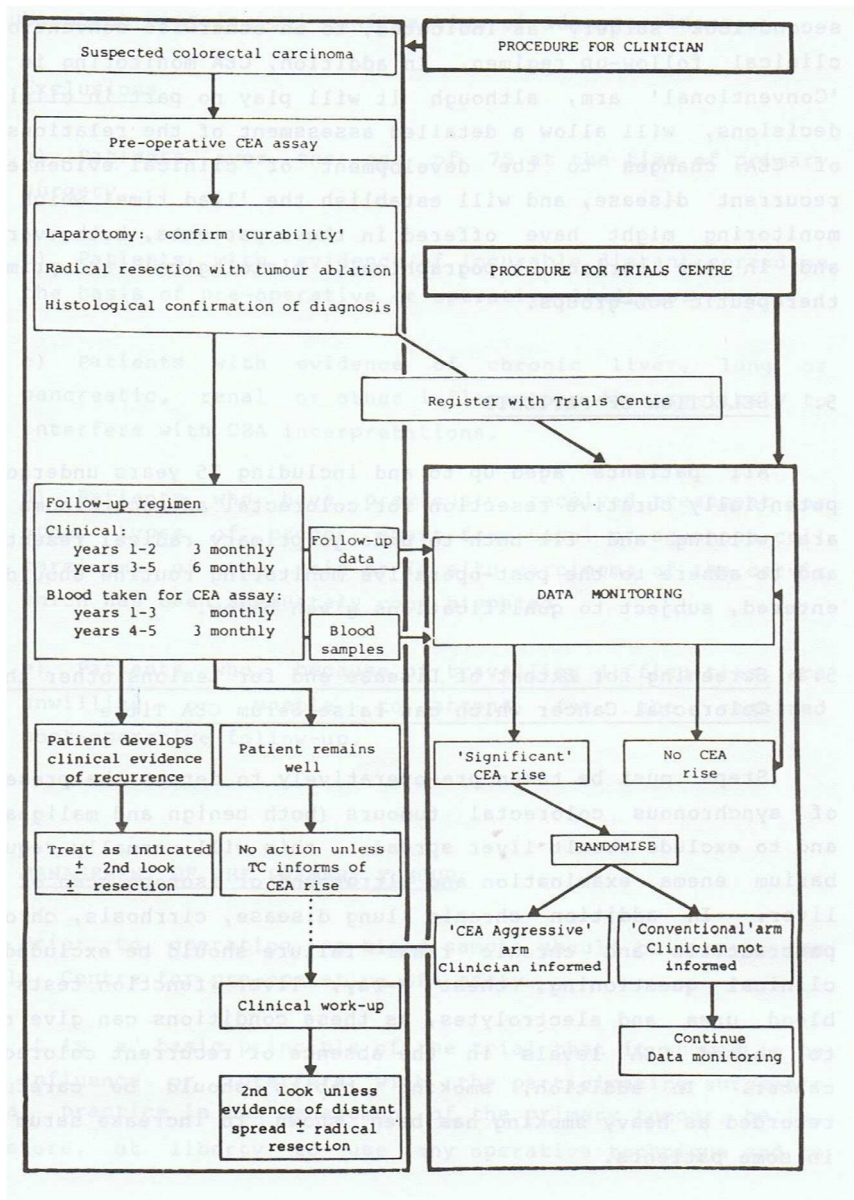


Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]  
159x223mm (200 x 200 DPI)

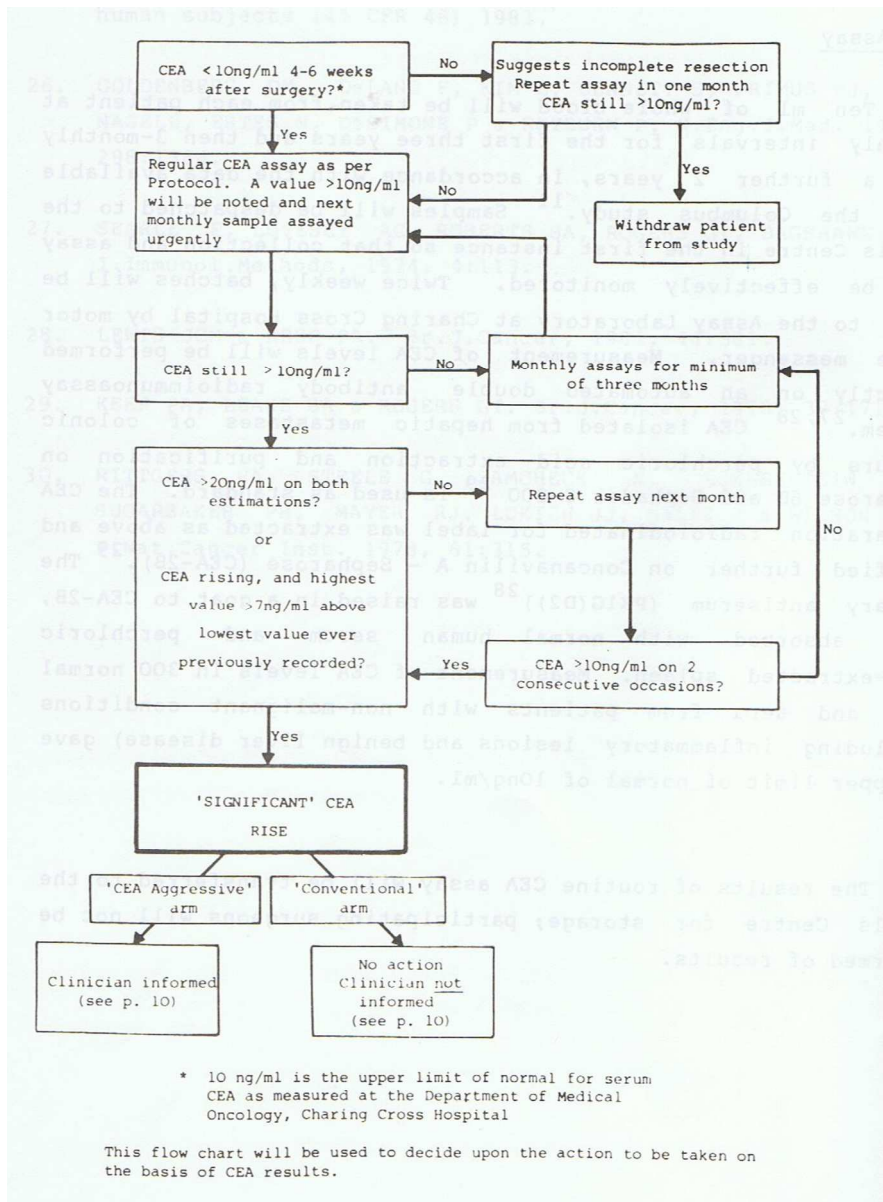


Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22] 159x215mm (200 x 200 DPI)

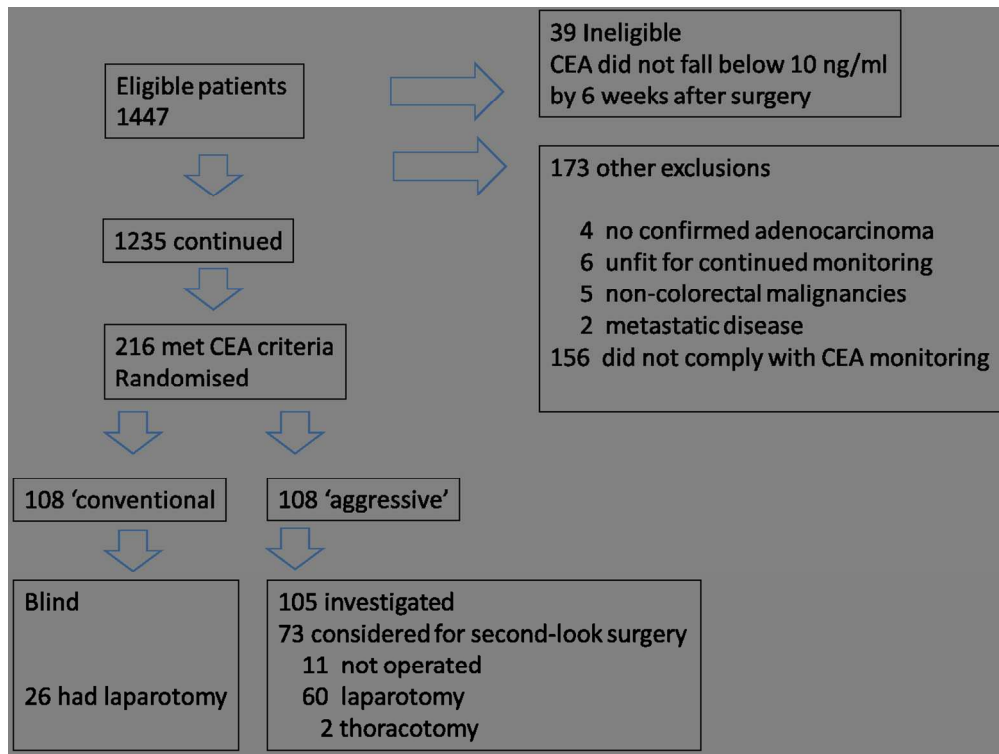


Figure 5. Flow chart of enrolled and ultimately randomised patients

View only

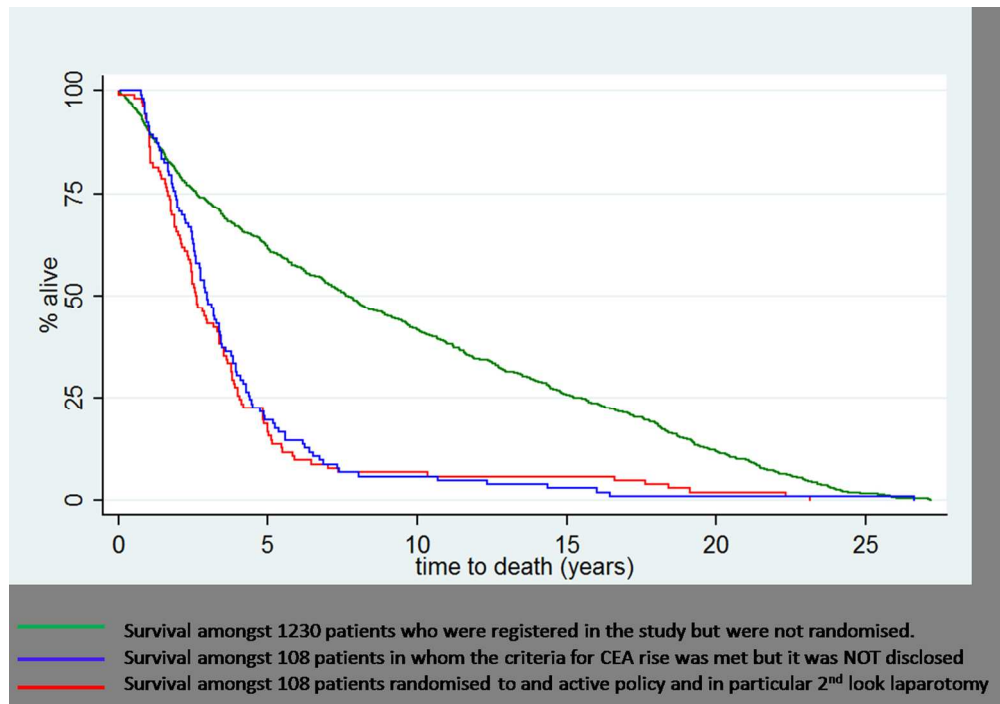


Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or 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.

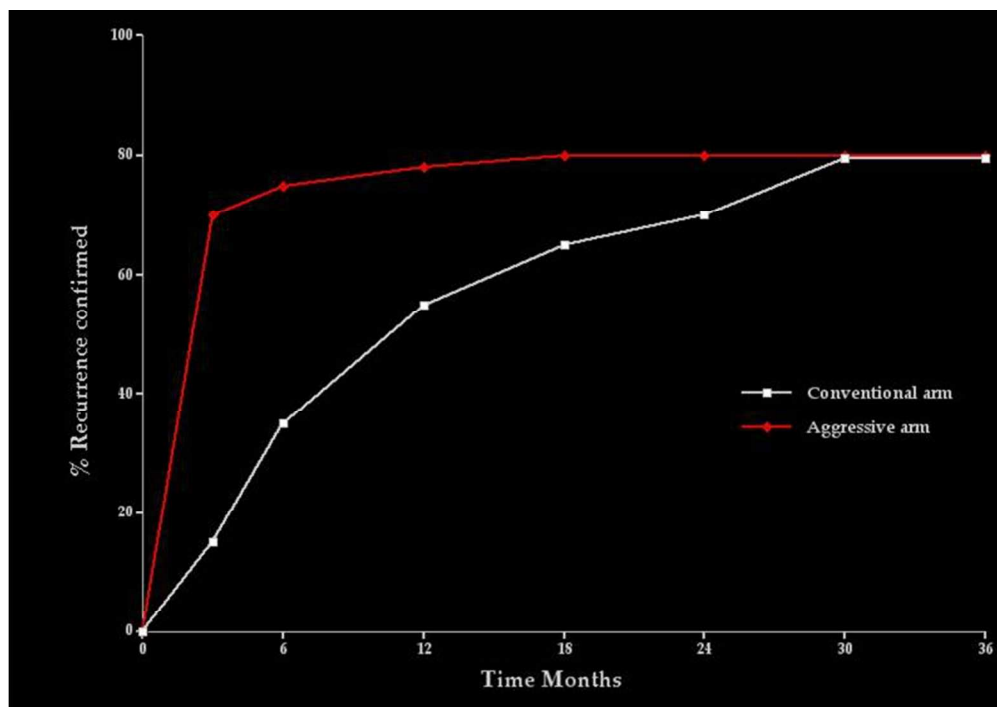


Figure 7. Illustration kindly provided by JMAN which was as used by him in presentations related to the analysis of the DMC in 1993. We have not verified the dates of detection but there is no reason to doubt them and it remains a valid illustration of the efficacy of CEA monitoring in detecting recurrence but does not alter the conclusion that second-look surgery prompted by it is ineffective in improving survival.  
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
<b>Title and abstract</b>						
	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	
<b>Introduction</b>						
Background and objectives	2a	Scientific background and explanation of rationale	5-6	4-9	None written	
	2b	Specific objectives or hypotheses	3	2	2	
<b>Methods</b>						
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			
<b>Results</b>						
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.
<b>Discussion</b>						
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			
<b>Other information</b>						
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	

1  
2 \* 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  
3 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  
4 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  
5 other CONSORT extensions, e.g. for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. See  
6 [www.consort-statement.org](http://www.consort-statement.org) for more details.  
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**The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004385.R1
Article Type:	Research
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; Imperial College London, Cardiac Surgery Russell, Christopher
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Colorectal surgery < SURGERY, Chemical pathology < PATHOLOGY, Adult oncology < ONCOLOGY, Adult gastroenterology < GASTROENTEROLOGY, CHEMICAL PATHOLOGY
<p>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.</p> <p>RIAT for public access.zip</p>	

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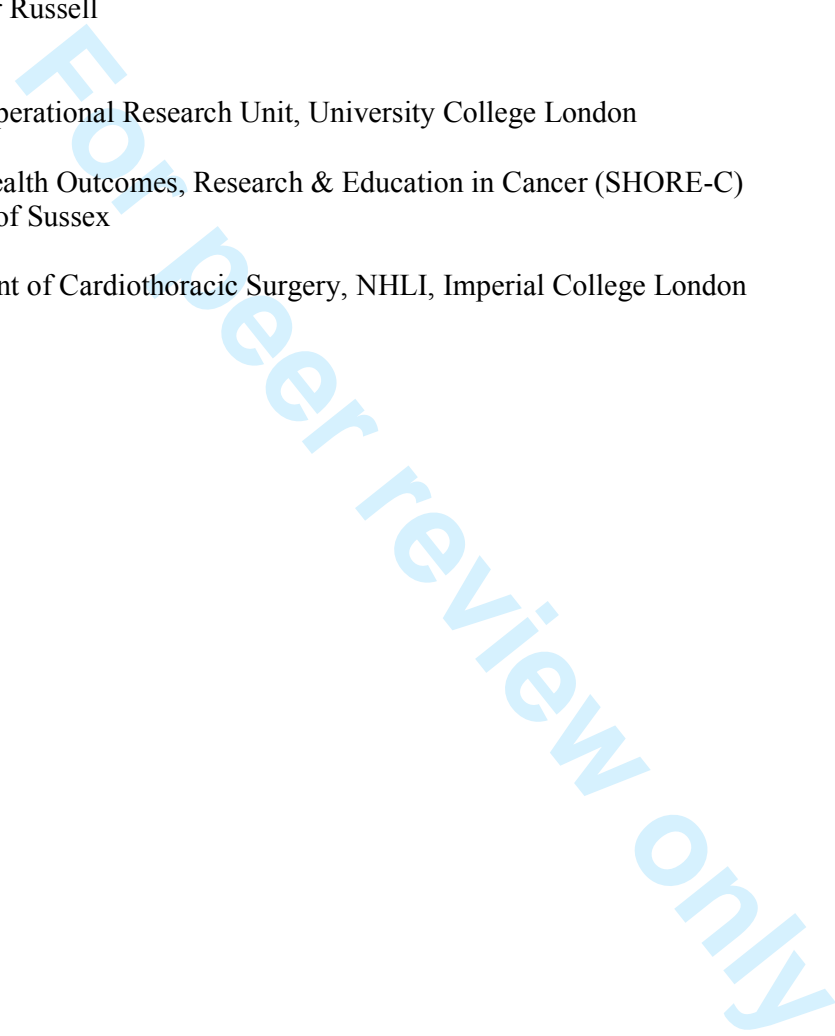
Title  
The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.

Tom Treasure<sup>1</sup>  
Kathryn Monson<sup>2</sup>  
Francesca Fiorentino<sup>3</sup>  
Christopher Russell

<sup>1</sup>Clinical Operational Research Unit, University College London

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University of Sussex

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#### 30 46 Contributor statement

31 47 TT instigated the recovery of the data, worked on the database recovery described in the  
32 48 manuscript and wrote the first and edited the final version of the manuscript.  
33 49 KM navigated the data files and worked on the database recovery described in the  
34 50 manuscript.  
35 51 FF performed the analysis of the recovered data and the presentation of the analysis.  
36 52 RCGR negotiated access to the data and with TT contacted and interviewed the members of  
37 53 the original trial team.  
38 54 All authors have read and contributed to successive iterations of the manuscript and approve  
39 55 the submitted version.  
40  
41 56

#### 42 57 Data sharing

43 58 We are prepared to share the data in our possession and to direct any applicants for stored  
44 59 data to the head of the trial centre where the data are still held.  
45  
46 60

#### 47 61 Acknowledgments

48 62 The RIAT authors are grateful to Jonathan Ledermann, Director of the Cancer Research UK  
49 63 & UCL Cancer Trials Centre, University College London, (where the CEA files were stored)  
50 64 and Sharon Forsyth for her assistance in accessing the CEA trial data and updating the Office  
51 65 of National Statistics records for death registration. The RIAT authors also met with the  
52 66 following persons who were members of the 1982 Working Party at the Cancer Research  
53 67 Campaign Clinical Trials Centre (CRC CTC) King's College Hospital Medical School,  
54 68 London and/or were listed as contributors in the 1994 manuscript from the CRC CTC at the  
55 69 Rayne Institute, 123 Coldharbour Lane, London SE5 9NU: M Baum, RHJ Begent, H Ellis, J  
56 70 Houghton, M Irving, CA Lennon, JMA Northover, WW Slack and CB Wood. We are  
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71 grateful to them for frank discussions concerning the progress of the study and the factors  
72 leading to its abandonment.  
73 FF is partly funded by the British Heart Foundation.  
74 None of the authors has a conflicts of interest.  
75

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1  
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3 76  
4 77 Abstract

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6 78 Objectives: in patients who have undergone a potentially curative resection of colorectal  
7 79 cancer does a 'second-look' operation to resect recurrence, prompted by monthly  
8 80 monitoring of carcinoembryonic antigen, confer a survival benefit?

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11 81 Design: randomised controlled trial

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13 82 Setting: 58 hospitals in the United Kingdom and Europe.

14  
15 83 Participants: from 1982 to 1993, 1447 patients were enrolled. Of these 216 met the  
16 84 criteria for CEA elevation and were randomised to 'Aggressive' or 'Conventional' arms.

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18 85 Interventions: 'second-look' surgery with intention to remove any recurrence discovered.

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21 86 Primary outcome measure: survival.

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23 87 Results: by February 1993, 91/108 patients had died in the 'Aggressive arm' and 88/108  
24 88 in the 'Conventional' arm (relative risk = 1.16, 95% CI 0.87-1.37). By 2011 a further 25  
25 89 randomised patients had died. Kaplan Meier analysis showed no difference in long-term  
26 90 survival.

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29 91 Conclusions: the trial was closed in 1993 following a recommendation from the Data  
30 92 Monitoring Committee that it was highly unlikely that any survival advantage would be  
31 93 demonstrated for CEA prompted second-look surgery. This conclusion was confirmed by  
32 94 repeat analysis after twenty years.

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97 Strengths and limitations of this study

98 • The CEA Second-Look Trial was a well-planned and carefully executed study with a  
99 clear question and a well-defined outcome of interest.

100 • Second-look surgery prompted by the best available indicator of recurrence at the  
101 time conferred no survival advantage.

102 • A further strength, and a reason to publish this trial now, is that it shows that  
103 randomised trials in surgery can be done and that the result may be contrary to the  
104 beliefs and expectations of practitioners based on their uncontrolled observations.

105 • A limitation is that present day means of detection, based on imaging and anatomical  
106 localisation, may detect patients with recurrence curable by surgery. It follows that  
107 the effectiveness of second-look surgery prompted by new imaging methods cannot  
108 be assumed but should be the subject of controlled trials.

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3 110 Introduction  
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5 112 It was observed during the 1970s that the outlook for patients with colorectal cancer was not  
6 113 good. Only one in four patients survived for five years after diagnosis and radical surgery was  
7 114 observed to be curative in under half of patients (1). Results had not improved in several  
8 115 decades.(2-4). Refinements in primary operative techniques had not made a difference(5)  
9 116 and it was considered unlikely that technical modifications would lead to improvement in  
10 117 survival following surgery.(1;2) Routine surgical follow-up had not led to further surgery  
11 118 being shown to be beneficial. Clinical evidence of recurrence usually meant that the tumour  
12 119 would be unresectable at second-look laparotomy(6) First-hand experience of members of the  
13 120 Carcinoembryonic antigen (CEA) Second-Look Trial development group was that of 180  
14 121 patients, followed up from six months to 15 years, at a total of 2319 out-patient clinic visits,  
15 122 only one patient could be considered to have had a potentially curative second-look  
16 123 operation. (7) To re-resect with prospect of benefit, recurrence had to be detected before it  
17 124 was clinically evident(4) but more pro-active clinical follow-up of asymptomatic patients by  
18 125 three monthly sigmoidoscopy, barium enema and chest X-ray (the methods available at the  
19 126 time) had failed to show improvement in 5-year survival.(8) Nevertheless, there had been  
20 127 several reports of 30% five-year survival in selected patients after radical resection of  
21 128 recurrent cancer(3;9;10) and resection was believed to sometimes lead to “cure”.(3;9-11)  
22 129

23 130 *Improving detection and treatment of recurrent disease: the context in 1982*  
24 131

25 132 The trial development group considered the evidence available at the time for methods of  
26 133 detecting recurrence early and a founding principle of the CEA Second-Look Trial was that  
27 134 early detection of recurrent tumour would only be justifiable if further treatment offered the  
28 135 prospect of benefit to the individual patient.(4) The evidence available to the group is  
29 136 outlined below.  
30 137

31 138 *The Wangenstein Approach:*

32 139 During the 1950s the systematic use of a policy-based second operation was reported.  
33 140 Patients at high risk of recurrence (those with Dukes' Stage C tumours) were re-operated on  
34 141 at 6-monthly intervals, resecting recurrence when found, until they were ‘tumour free’. If  
35 142 cancer had been found the patients were scheduled for 3<sup>rd</sup> and more “looks”, up to six further  
36 143 abdominal operations, “before the abdomen was free of cancer”. Once a patient had  
37 144 undergone a negative laparotomy, no more surgery was recommended. Sixty-four patients  
38 145 with colon or rectal cancer were managed in this way. In 35 (55%) of them the “second-  
39 146 look” laparotomy was negative for the discovery of recurrent cancer, seven of whom  
40 147 subsequently had clinical recurrence. There were four (6%) operative deaths.(12) The CEA  
41 148 trialists concluded that this ‘blanket second-look’ policy might have produced some “cures”  
42 149 but entailed high rates of negative laparotomy and an unacceptable operative mortality  
43 150 rate.(4)  
44 151

45 152 Figure 2 from Wangenstein 1954  
46 153

47 154 *The CEA-prompted Second-Look Approach*

48 155 CEA had been shown to detect recurrence of colorectal cancer following surgery.(13-18)  
49 156 CEA rose, on average, four months prior to clinical evidence of recurrence(14) and there  
50 157 were reports of the use of serial serum carcinoembryonic antigen (CEA) assays to detect  
51 158 asymptomatic recurrences in the belief that curative resection would be possible more  
52 159 frequently.(13-15) Several groups used CEA in this way, and found low false positive  
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3 160 rates(6;19) and the resectability rate of the recurrence was higher than when clinical criteria  
4 161 were used to prompt re-operation.(6) In the largest published experience of CEA in a post-  
5 162 operative monitoring role(6;13) resectable recurrent tumour was found in 70% in whom re-  
6 163 operation was prompted by a rise in the serum CEA compared with a quarter of patients  
7 164 undergoing second-look laparotomy prompted by clinical indications. Others had not found  
8 165 CEA to be useful in this post-operative monitoring role. Even if efficacy of CEA detected  
9 166 recurrence was accepted, there was also the unresolved question of effectiveness: if more  
10 167 patients were detected and there were more instances of resectable recurrence, did that lead to  
11 168 better survival and patient benefit? The conflicting interpretations of observational data  
12 169 resulted in calls for trials(13;19;20) including within a 1981 NIH Consensus Statement.(18)  
13  
14 170  
15 171

16 172 The objective of the CEA Second-Look Surgery Trial was to determine whether, following  
17 173 potentially curative primary surgery for colorectal cancer, mortality could be decreased by a  
18 174 policy of second-look surgery prompted by rising serum carcinoembryonic antigen (CEA).  
19 175 The trial ran from 1982 to 1993. The main result, that there was no survival advantage, was  
20 176 reported in 1994 to the British Oncological Association(21) and was published in a letter to  
21 177 the Journal of the American Medical Association.(22)  
22  
23 178

24 179 Surgery for colorectal cancer recurrence has since become routine both in the form of hepatic  
25 180 resection(23) and pulmonary metastasectomy(24) but without evidence from controlled trials  
26 181 for either practice.(25) When doubts were raised about the security of the evidence in the  
27 182 British Medical Journal in 2007(26) a general belief existed that randomised controlled trials  
28 183 of the effectiveness of resection of liver or lung metastases were not possible and were not  
29 184 needed. These paired beliefs are brought into question by the CEA Second-Look Trial: a  
30 185 randomised trial was done and the presumed benefit of surgery for cancer recurrence was not  
31 186 seen.(21;22)  
32  
33 187

#### 34 188 *Abandonment of the trial in 1994 and gaining access to the data in 2011*

35 189 The RIAT restorative authors had been involved in various studies related to surgery for  
36 190 disseminated colorectal cancer(26-28) including a conundrum as to whether discovery of an  
37 191 elevated CEA assay should prompt or be considered a contra-indication to pulmonary  
38 192 metastasectomy.(29) We knew the CEA trial to have been enrolling patients in the 1980s but  
39 193 when we searched the literature for the result of the trial we learned that it had been  
40 194 abandoned in 1994. In 2009 we contacted the chief investigator of the trial and the present  
41 195 director of the unit. The data were initially thought to be irretrievably lost or irrecoverable.  
42 196 However, staff at the trials centre retrieved archived CEA electronic files and the death data  
43 197 were updated. We gained access to anonymised electronic data in 2011. The process of data  
44 198 restoration is described later.  
45  
46 199

47 200 Amongst the documents were listed the members of the trial development group in the 1982  
48 201 protocol(4) and the contributors to the 1994 manuscript.(30) None of these individuals  
49 202 expressed an interest in resuming work on the trial or were in a position to do so. When we  
50 203 contacted them later to share the restored data with them no one raised any objection but on  
51 204 the contrary encouraged us to publish their findings.  
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54 206 Figure 1 Working Party from the 1982 Protocol  
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3 211 Methods: trial intent and design

4 212 *The recruitment intentions and the trial protocol as presented here are essentially as written*  
5 213 *in the manuscript prepared in 1994 with the intention of publishing the trial.(30) The text has*  
6 214 *been edited by the RIAT authors but no new material has been introduced.*  
7

8 215 The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years  
9 216 and to follow them for five years. The study was specifically designed with late  
10 217 randomisation in order to maximise statistical power. It was originally intended to recruit  
11 218 2,000 patients with the anticipation that about 25% would show a CEA rise as the first  
12 219 evidence of possible recurrence. This number would have provided 95% power to detect an  
13 220 improvement in two year survival from the second-look procedure from 25% to 55% at  
14 221  $\alpha=0.05$ . The protocol stated that for the trial to be stopped prematurely very stringent levels  
15 222 of significance ( $p<0.001$ ) would be used.  
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18 223

19 224 The CEA trial design was devised so that clinical follow-up would remain unbiased, and  
20 225 allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent  
21 226 colorectal cancer. After potentially curative surgery for colorectal cancer, all eligible patients  
22 227 were to be monitored identically using conventional clinical follow-up together with regular  
23 228 CEA assay, performed centrally. Clinicians would not be informed of the result. When a  
24 229 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into  
25 230 either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm,  
26 231 the clinician would immediately be informed of the CEA rise so that the patient could be  
27 232 urgently screened to exclude widespread metastatic disease or a non-malignant cause for the  
28 233 CEA rise. If neither was found, and the patient was medically fit for operation, second-look  
29 234 surgery to locate and remove any treatable recurrence was mandatory. In the case of patients  
30 235 in the 'Conventional' arm, the clinician would not be informed of the 'significant' CEA rise  
31 236 nor of subsequent randomisation to not have the CEA rise revealed.  
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35 238 The primary outcome was survival based on death certification through the Office of  
36 239 Population Censuses and Surveys (OPCS) (now called the Office for National Statistics  
37 240 (ONS)). No subset analyses were planned.  
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39 241

40 242 The intention as stated in the protocol was that the trial would produce:  
41

42 243

- 43 244 a) a definitive answer concerning the effectiveness of CEA-prompted second-look  
44 245 surgery to improve survival  
45 246 b) an accurate picture of the 'lead time' produced by CEA compared to clinically  
46 247 indicated second-look surgery  
47 248 c) further data relating CEA levels to tumour histology and topography, and  
48 249 d) a large data base on the natural history of colorectal cancer.(4)  
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50 250

51 251 The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements  
52 252 give no indication as to the precise nature of analyses that might follow and are regarded as  
53 253 opportunities for explanatory subset analyses which were not in the event carried out.  
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57 256 Methods: the conduct of the trial 1982 to 1993  
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3 258 The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical  
4 259 Trials Centre at King's College Hospital. CEA assays were performed using a  
5 260 radioimmunoassay technique at a single centre at Charing Cross Hospital.  
6 261  
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### 8 263 *Selection of patients*

9 264 All patients up to the age of 76 who had undergone a potentially curative resection for  
10 265 adenocarcinoma of the colon or rectum and who were fit and willing to adhere to the post-  
11 266 operative monitoring routine were eligible for the study. Patients were excluded if there was  
12 267 evidence of incurable distant spread, either pre-operatively or during the primary operation,  
13 268 or if the CEA level failed to return to the normal range (<10 ng/ml) within six weeks of  
14 269 primary surgery. Patients who had previously received treatment for other types of cancer,  
15 270 apart from basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix  
16 271 adequately cone biopsied, were excluded from the study.  
17 272  
18 273

### 19 274 *Management of the primary tumour*

20 275 A pre-operative blood sample for CEA assay was taken from all patients with suspected  
21 276 colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. This was a  
22 277 pragmatically designed study so each surgeon was at liberty to use their normal operative  
23 278 technique and to employ peri-, or post-operative radiotherapy, or adjuvant chemotherapy as  
24 279 was seen fit, however they were asked to remain consistent regarding the treatment used for  
25 280 any particular type of disease. If at laparotomy, a potentially curative resection was  
26 281 performed and subsequent histology confirmed the diagnosis of adenocarcinoma, the patient  
27 282 was given a full explanation of the study and could be registered.  
28 283

### 29 284 *Baseline data*

30 285 Following informed consent, the surgeon carried out investigations to detect the presence of  
31 286 synchronous colorectal tumours (both benign and malignant) and to exclude occult liver  
32 287 spread; (usually barium enema examination and ultrasound or CT scan of the liver). In  
33 288 addition, factors that could give raised CEA levels in the absence of recurrent colorectal  
34 289 cancer, such as chronic lung disease, cirrhosis, chronic pancreatitis, and chronic renal  
35 290 failure were excluded by clinical questioning, chest x-ray, liver function tests, blood urea and  
36 291 electrolytes. Smoking habits and alcohol consumption were also recorded as heavy smoking  
37 292 or drinking, or a change in these habits, can influence CEA levels.  
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### 41 296 *Patient Entry*

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44 299

45 300 Figure 3: Trial flow diagram  
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### 48 303 *Monitoring of Patients*

49 304 Clinical follow-up of all patients continued in an identical manner (three monthly for the first  
50 305 two years and six monthly for the next three years) whilst blood for CEA assay was drawn  
51 306 monthly for the first three years and three monthly for the next two years. If the patient  
52 307 remained well and the CEA was within normal limits as defined by a pre-tested algorithm,  
53 308 monitoring continued according to the schedule.  
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3 308 *CEA assay*

4 309 Ten mls of whole blood were taken from each patient. The serum was separated and sent to  
5 310 the Trials Centre in special plastic phials. After logging receipt, the samples were forwarded  
6 311 to the Medical Oncology Department at Charing Cross Hospital for assay. The results were  
7 312 returned to the Trials Centre for recording and action if appropriate. This centralised system  
8 313 ensured that all participating clinicians were kept blind to the CEA results for their patients.  
9 314 It also ensured quality control of the CEA assay as there was no possibility of inter-laboratory  
10 315 variation.

11 316  
12 317 Serum CEA values were measured by double antibody radioimmunoassay.(31-33) A bank of  
13 318 serum samples has been retained at -20°C.

14 319

15 320 *Monitoring assay compliance pre-randomisation*

16 321 Throughout the trial, compliance with blood sampling was monitored by the secretariat.  
17 322 Clinicians were reminded each month of the patients for whom samples were due; those who  
18 323 had missed the previous visit were highlighted as urgent. The percentage compliance for  
19 324 each participating patient was calculated as the number of samples received divided by those  
20 325 expected x 100. The median time between samples was also calculated. Failure to achieve  
21 326 50% or less of the expected samples was defined as poor compliance. Since the sensitivity to  
22 327 detect CEA rises in such patients was greatly reduced and they were excluded from  
23 328 randomisation.

24 329

25 330

26 331 *'Significant' Rises in CEA*

27 332 A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on  
28 333 two successive occasions and one of the following conditions was also met: the CEA level  
29 334 was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the  
30 335 highest value was more than 7ng/ml above the lowest value ever recorded.

31 336 If a 'significant' rise in CEA occurred, the record of the patient was reviewed at the Trials  
32 337 Centre and provided no evidence of suspected colorectal or other disease was recorded in the  
33 338 CRF, the patient was randomised either into an 'Aggressive' or 'Conventional' arm.

34 339

35 340 Figure 4: CEA algorithm

36 341

37 342 *Randomisation*

38 343 Patients were randomised equally between the two arms (1:1). Patients whose compliance  
39 344 was between 50 and 70% or whose immediate post-operative sample had not been received  
40 345 within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was  
41 346 also stratified by participating clinician. A block size of two was used in order to maintain as  
42 347 close a balance as possible between the two treatment arms. .

43 348

44 349 If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise  
45 350 immediately by telephone from the trial centre and subsequently in writing and was requested  
46 351 to contact the patient urgently. Patients were informed of their situation including the fact  
47 352 that they had been randomised within the trial to undergo a second-look procedure. This was  
48 353 then undertaken if the patient gave informed consent. The surgeon carried out a full clinical  
49 354 work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g., change in  
50 355 smoking or drinking habit) and to identify any incurable distant spread. In the absence of  
51 356 these conditions the surgeon undertook a mini-laparotomy, proceeding to full laparotomy with  
52 357 macroscopic clearance of disease, should this be possible.

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3 358 For patients randomised to the 'Conventional' arm no further action was taken; the clinician  
4 359 was not informed that the CEA had risen nor that the patient had been randomised.  
5 360

6 361 If at any stage a patient in the study developed clinical evidence of recurrent disease the  
7 362 clinician was at liberty to manage the patient according to usual practice. If the disease was  
8 363 in the abdomen and was thought to be treatable by a second-look operation with re-resection,  
9 364 this was perfectly acceptable. The clinician was blind as to whether such patients had been  
10 365 randomised to the 'Conventional' arm of the trial or had not been randomised because the  
11 366 CEA had failed to denote the presence of recurrent disease.  
12 367

#### 13 368 *Second-Look Laparotomy*

14 369 The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate  
15 370 any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was  
16 371 detected all that was required prior to closure, was biopsy. Otherwise following a full  
17 372 excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the  
18 373 small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis  
19 374 was undertaken. The liver was fully mobilised to determine whether any tumour was present.  
20 375 Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then  
21 376 carried out with the objective of total extirpation of all recurrence. Complete data recording  
22 377 of the procedure along with the results of the histology of all potentially involved sites was  
23 378 required by the trial's office.  
24 379

25 380 For patients in whom a radical resection was achieved after second-look surgery (motivated  
26 381 either on clinical information or because the patient had been randomised to the 'Aggressive'  
27 382 arm) the follow-up schedules for clinical examination and blood sampling reverted to those  
28 383 following the primary operation. However, for patients randomised to the 'Aggressive' arm,  
29 384 clinicians were immediately notified of any further CEA levels above 10ng/ml.  
30 385

#### 31 386 *Death*

32 387 Every patient registered onto the study was 'flagged' with the Office of Population Censuses  
33 388 and Surveys (OPCS) who provide automatic notification of date of death. This enabled the  
34 389 trial centre to receive certified cause of death for all patients.  
35 390

#### 36 391 *Trial oversight*

37 392 A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not  
38 393 entering patients into the trial was asked to review the data after the first 100 patients had  
39 394 been randomised, which occurred in January 1988, and again after 200 patients had been  
40 395 randomised in February 1993, at which point it was recommended that the trial was stopped  
41 396 since it was very unlikely that any clinically important advantage would be demonstrated for  
42 397 patients undergoing second-look surgery.  
43 398

#### 44 399 *Methods of the RIAT process*

##### 45 400 *The data*

46 401 The RIAT restorative authors had been warned by the statisticians called in to look at the data  
47 402 in 2003-4 that "the databases were corrupted with key variables no longer abstractable" and  
48 403 that they could not be analysed without a lot of work.(34;35) We found that the data on  
49 404 paper and on file were accessible and we had no reason to doubt the veracity of individual  
50 405 items. We found that the electronic files had numerous problems with formatting which  
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3 408 made the files on the 1447 individual patients difficult to handle but that the data entries were  
4 409 not themselves corrupted.

5 410  
6 411 One of the RIAT restorative authors (KM) had worked in the trials units during the time the  
7 412 CEA Trial data were being accrued and knew the systems in use and their changes but was  
8 413 not directly involved in this trial at any stage.

9 414  
10 415 The questions raised and the problems encountered, were resolved as follows:  
11 416

- 12 417 • The codes indicating that a patient had met the criteria for CEA elevation and  
13 418 whether they were randomised to 'active' or 'Conventional' arm were preserved and  
14 419 tallied with the number in the 1994 manuscript.(30)  
15 420
- 16 421 • There were variations in the way dates were recorded in the database. There had been  
17 422 migrations of data from a 'Prime' server using 'Universe' to 'Excel' and the  
18 423 interpretation of the present authors, with information from contemporary witnesses  
19 424 was that in undertaking the task operators did not always correctly specify these data  
20 425 as 'dates' when importing, and/or allowed them to be converted to American date  
21 426 formats. These errors prevented calculations and would have defeated running a  
22 427 survival analysis without correction of the file entries. The dates were however  
23 428 visually readable and not 'corrupt'. Some could be corrected by running current  
24 429 versions of software. Others were manually corrected by re-entering them in a  
25 430 Microsoft date format. Paper records were available to resolve uncertainties.  
26 431
- 27 432 • The next problem was in linking these three groups of patients (randomised to  
28 433 'aggressive', randomised to 'conventional' and not randomised) to the dates for  
29 434 survival analysis. Individual patients were uniquely identified in the files by seven  
30 435 digit strings to which letters had been added at the beginning and end, possibly for  
31 436 trial administrators' checklists or subgroup identification. Once we had established  
32 437 that the initial and terminal letters were redundant for analysis of the primary  
33 438 endpoint, we were able to write code to restore the seven digit strings.  
34 439
- 35 440 • It was evident that the seven digits did not represent a simple sequence but certain  
36 441 positions identified particular characteristics, such as participating centre. We  
37 442 recognised a consistent pattern of mismatch in the fourth digit, a zero in one file was  
38 443 an 8 in the other with all other digits remaining the same. It was suggested to us that  
39 444 the fourth digit replacement was used to identify patients suitable for *post hoc*  
40 445 subgroup analyses but no documentation was found to confirm this. By checking  
41 446 back to the dates of birth we were able to confirm that this systematic correction  
42 447 resolved the problem and most of the data were then usable.  
43 448
- 44 449 • By ranking all the data in the paired files for line by line visual inspection residual  
45 450 discrepancies were identified. Scrutinising the digit strings allowed for seven of the  
46 451 remaining eight pairs to be reconciled and verified on dates of birth. We failed to  
47 452 resolve only one out of 1447 records in each file. This patient had not been  
48 453 randomised.  
49 454
- 50 455 • Inspection of the accrual of death dates was discontinuous for a couple of years  
51 456 suggesting a lapse in either recovery or entry. The current trials centre obtained  
52 457 permission to re-run the Office for National Statistics (ONS) search in July 2012.  
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458  
 459 In summary, we identified several problems but they were systematic and not random (we  
 460 would not use the value laden word 'corrupted'). We were able to rectify the formatting  
 461 errors and verify that the data used for our analysis were correct. The Kaplan Meier analysis  
 462 was re-run.

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464

465

466 Results

467

468 *The original main results 1994*

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

479 Figure 5

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

486

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

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

492

493

494

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 <sup>1</sup>	36 (33.3)	38 (35.2)
Dukes' C <sup>2</sup>	17 (15.7)	10 ( 9.3)
Missing	4 ( 3.7)	6 ( 5.6)



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4 496  
5 497 The stage mix of 980 patients who were eligible for inclusion in the randomised trial but who  
6 498 did not have a CEA rise as defined was Dukes' A 15.1%, B 55.2%, C1 23.3%, C2 6.4%.

7 499  
8 500 Of the patients randomised to the 'Aggressive' arm 83 (77%) had recurrent cancer identified  
9 501 and 62 (57%) patients had 'second-look' surgery. In patients randomised to the  
10 502 'Conventional' arm 89 (82%) had developed recurrent disease by the date of analysis. In  
11 503 these 26 (24%) second-look procedures were undertaken. By February 1993, 91/108 in the  
12 504 the 'Aggressive arm' had died and 88/108 patients had died in the 'Conventional' arm  
13 505 (relative risk = 1.16, 95% CI 0.87-1.37).(30) It was considered by the data monitoring  
14 506 committee to be "highly unlikely that any survival advantage would be demonstrated for  
15 507 patients undergoing second-look surgery". This was communicated to the trial centre.

16 508

#### 17 509 *RIAT restoration and updated survival analysis*

18 510 The data were restored by the RIAT authors for 1446 of 1447 patients to the extent that the  
19 511 RIAT authors were confident of their dates of birth, death and whether they met criteria for  
20 512 entry into the controlled trial and then to which arm they were allocated.

21 513

22 514 The electronic records were intact with respect to the identity of the patients, which patients  
23 515 had reached the criteria for randomisation, and the trial arm to which they had been randomly  
24 516 allocated for all 216 patients who were randomised. The sex, age, primary site and Dukes'  
25 517 stage as recorded in the 1994 manuscript are shown in Table 1.

26 518

27 519 Certification of death was obtained from ONS on behalf of the RIAT restorative authors for  
28 520 204 of 216 randomised patients who died between 17/10/1983 and 08/09/2011. There were  
29 521 equal numbers of patients in the two arms (108) and equal numbers of death dates were  
30 522 retrieved (102). We also have dates of death in 862 of the 1230 patients who were not  
31 523 randomised. Kaplan Meier analysis in these three groups is shown in Figure 6, showing  
32 524 survival of the 1230 participants who entered the trial but were not randomised the 108  
33 525 participants in each arm randomised to have the CEA disclosed or not disclosed to the  
34 526 surgeon.

35 527

36 528 Figure 6 Kaplan Meier analysis

37 529

38 530 The lead time conferred by CEA monitoring, defined as the median time to clinically  
39 531 detected disease for patients randomised to the 'Conventional' arm, was 323 days (SE 60;  
40 532 95% confidence interval (CI) 203-443). This analysis included censored observations on 23  
41 533 patients, however only five of these had a censored time less than the lead time. It was  
42 534 regarded as unlikely, therefore, that the lead time would decrease as further events occur. The  
43 535 analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12  
44 536 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs  
45 537 44% and 97% vs 70% at a year. The RIAT authors did not repeat this analysis.

46 538

#### 47 539 Discussion

48 540 We have restored data sufficient to achieve the primary outcome of interest as specified by  
49 541 the CEA trialists:

50 542 "Does a policy of CEA-prompted second-look surgery following 'curative' resection  
51 543 of colorectal cancer produce a decrease in morbidity and mortality due to tumour  
52 544 recurrence, despite sequelae of second look surgery?"



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4 546 The answer is that acting on CEA elevation by second-look surgery did not reduce mortality  
5 547 compared with patients in whom similar CEA elevation remained unknown. This negative  
6 548 finding led to the closing of the trial in 1994(21;22) and we confirm it here. There was small  
7 549 non-significant excess of deaths in the ‘Aggressive’ arm. The burden of morbidity  
8 550 attributable to the greater number of investigations and operations was not captured by the  
9 551 trial protocol.

10 552

11 553 The second planned analysis was to obtain an accurate picture of the ‘lead time’ produced by  
12 554 CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up  
13 555 patients considerably sooner than the clinical methods available at the time by about six  
14 556 months to a year.

15 557

16 558 CEA monitoring is currently used by some for this purpose but in development of the  
17 559 PulMiCC trial we found variability in its use and inconsistency in the threshold used.(29)  
18 560 Other methods of investigation (MRI, PET and improved CT and echo) are now used to  
19 561 detect recurrence before it is clinically evident. It cannot be presumed, and on the basis of  
20 562 the CEA Second-Look Trial results there is doubt, that earlier detection by these newer  
21 563 methods, leading to further surgery, leads to better outcomes.

22 564

23 565 The third and fourth intentions set out by the CEA trialists were c) to obtain further data  
24 566 relating CEA levels to tumour histology and topography and d) a large data base on the  
25 567 natural history of colorectal cancer. Multiple CEA assay results exist in the data we hold for  
26 568 1446 patients and it would be possible to link these to survival as a result of the RIAT  
27 569 restorative work..

28 570

29 571 With respect to the natural history of colorectal cancer although we trust the death  
30 572 certification data for the date of death it has been shown that “at least a third of all death  
31 573 certificates are likely to be incorrect”(36). No doubt aware of this and seeking much more  
32 574 detailed information, the CEA Trialists had asked for detailed post-mortem examinations.  
33 575 Given the many differences in cancer evaluation and imaging in the intervening thirty years  
34 576 we would be cautious about their value now.

35 577

36 578 It appears that it was disagreement concerning explanatory analyses which contributed to the  
37 579 failure to publish the primary outcome of interest.(30) The purpose of such analyses is to  
38 580 discover subsets of patients in whom there was a benefit from the intervention under  
39 581 evaluation and to thus determine the characteristics of patients in whom the intervention  
40 582 might have had a beneficial effect by analysis of mediators and moderators.(37) There is a  
41 583 general objection to this exercise because it can lead to spurious associations.(38;39)  
42 584 Furthermore when there is no overall benefit found, as in the CEA Second-Look Trial, any  
43 585 subgroup(s) where there is a positive association between intervention and outcome must be  
44 586 balanced by one or more other groups where there was net harm. There were no completed  
45 587 subset analyses in 1994 and we have not attempted any in restoring the trial.

46 587

47 588 The answer to the primary research question was clear in 1993 and was the explicit reason for  
48 589 stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery  
49 590 had been missed and in the absence of benefit there was net harm being done to the patients.  
50 591 We cannot say whether this is inevitability associated with any form of second-look surgery  
51 592 for colorectal cancer or whether these findings will apply to any other means of selecting

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3 593 patients for second-look surgery. The forms of second look surgery now widely practiced in  
4 594 colorectal cancer are liver and lung resection of metastases.  
5 595

- 6 596
- 7 597 • Full mobilisation of the liver at second-look laparotomy was included in the CEA  
8 598 Trial protocol. Hepatic resection has entered routine practice based on observational  
9 599 data(40) and an opportunity to do a randomised trial, for which a power calculation  
10 600 was proposed in 1992 from the Mayo Clinic(41) was not taken.(23)
  - 11 601 • Two patients had a thoracotomy prompted by CEA elevation. Pulmonary  
12 602 metastasectomy for colorectal cancer is, after primary lung cancer, the second  
13 603 commonest thoracic cancer operation and is the subject of an ongoing randomised  
14 604 controlled trial.(42)

15 605  
16 606 If the CEA Trial findings can be generalised, and there is no obvious reason in principle why  
17 607 they should not be, it would suggest that more critical scrutiny of the evidence base that was  
18 608 used to bring surgery for advanced colorectal cancer, and specifically liver and lung  
19 609 metastasectomy into practice is warranted.(23;28) The CEA Trial was a well-conceived and  
20 610 meticulously executed randomised trial and we hope that publishing it now more than twenty  
21 611 years after its completion will indicate the possibility of more randomised trials in  
22 surgery.(43)  
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3 612 Legends

4 613

5 614 Figure 1. The “Working Party” that produced the protocol in 1982 for the CEA Second-Look  
6 615 Surgery trial.(4)

7 616

8 617 Figure 2. Illustration of operative findings in six successive operations seeking recurrence of  
9 618 colorectal cancer.(12)

10 619

11 620 Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.(4)

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13 622 Figure 4. Decision making algorithm for CEA to trigger second-look surgery.(12)

14 623

15 624 Figure 5. Flow chart of enrolled and ultimately randomised patients. ‘Blind’ in the bottom left  
16 625 box means that the clinical teams were unaware of the elevated CEA discovered and were  
17 626 unaware that the patients have been randomised. They were indistinguishable amongst the  
18 627 1230 non-randomised patients who were being followed-up. (See Figure 6)

19 628

20 629 Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446)  
21 630 following potentially curative colorectal cancer surgery. Patients who had CEA elevation  
22 631 according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA  
23 632 revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from  
24 633 Office for National Statistics in 104/108 in each arm. The green line is for all other patients.  
25 634 (N=862 of 1230) Some would have had clinically evident early recurrence precluding  
26 635 randomisation. The initial plateau is an illustration of a death free interval(44) or “immortal  
27 636 time bias”(45) Patients in prospective studies may have a built in obligatory survival time  
28 637 from some starting point in order to attain the requirements to be included in the data set.  
29 638 This is an artefact but may be absorbed into survival time adding to and not readily  
30 639 distinguished from survival time attributed to treatment.

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

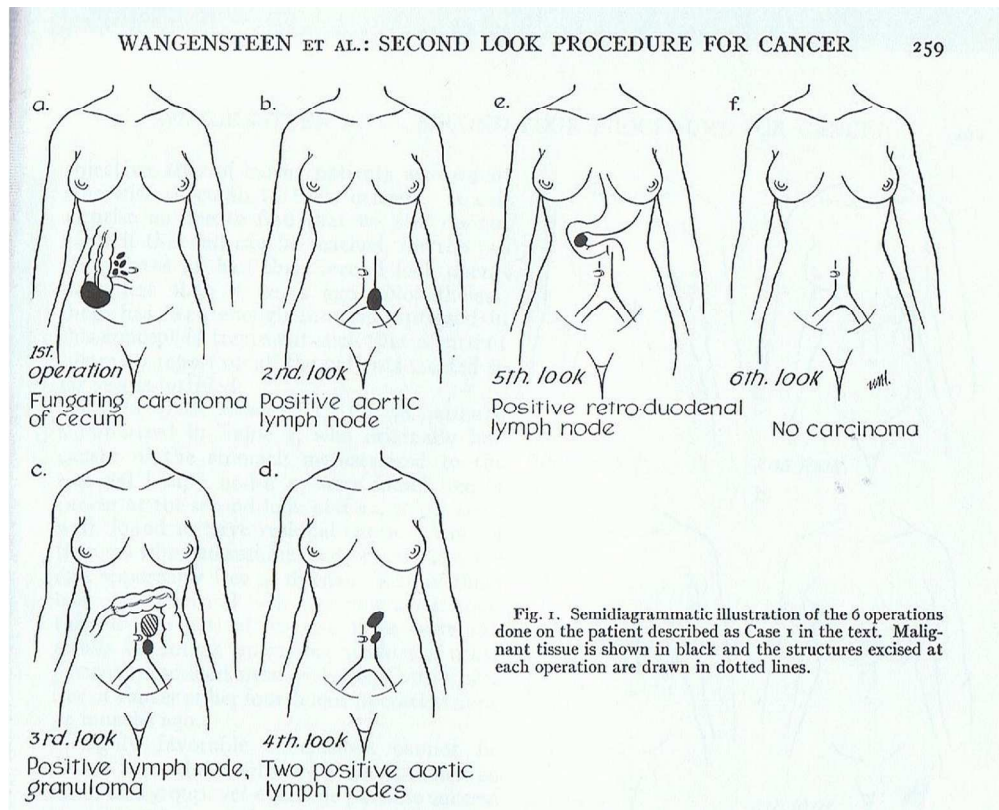


Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]  
111x90mm (300 x 300 DPI)

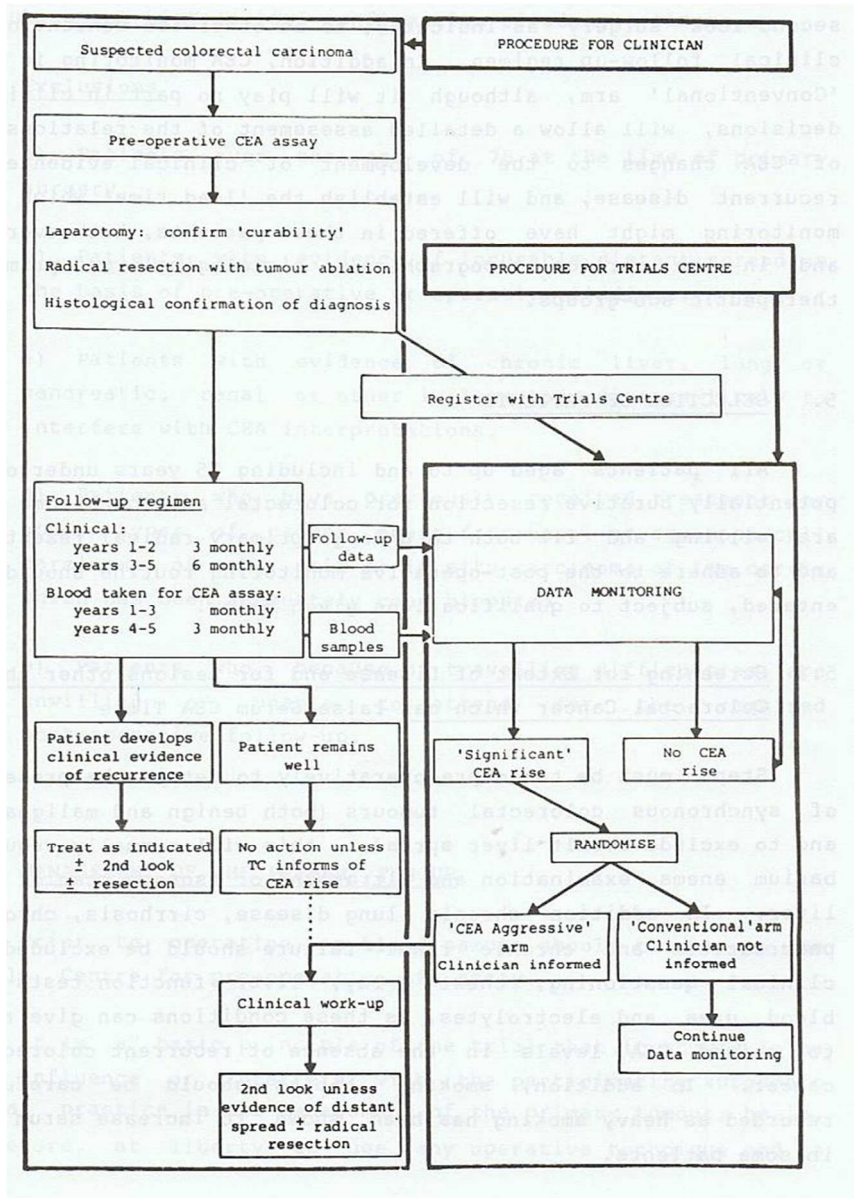


Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]  
64x90mm (300 x 300 DPI)

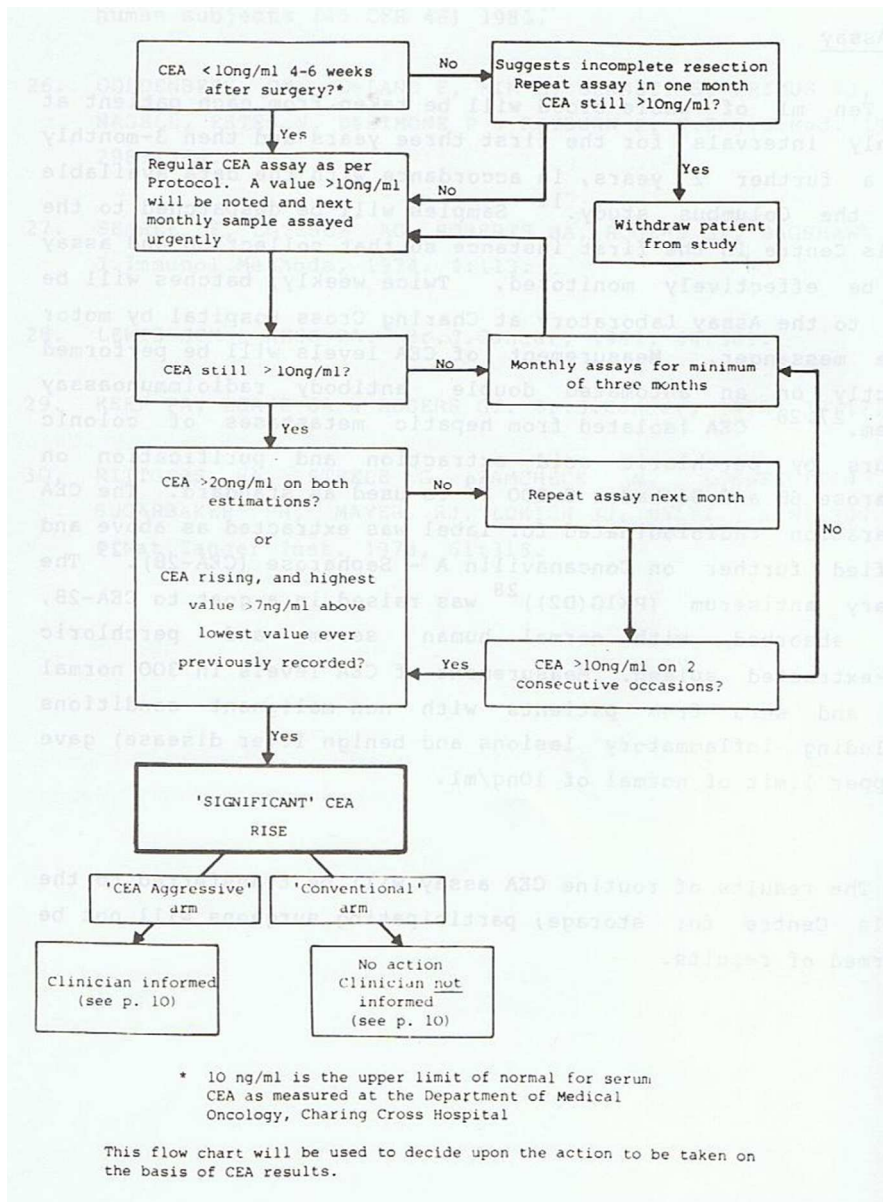


Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22] 66x90mm (300 x 300 DPI)

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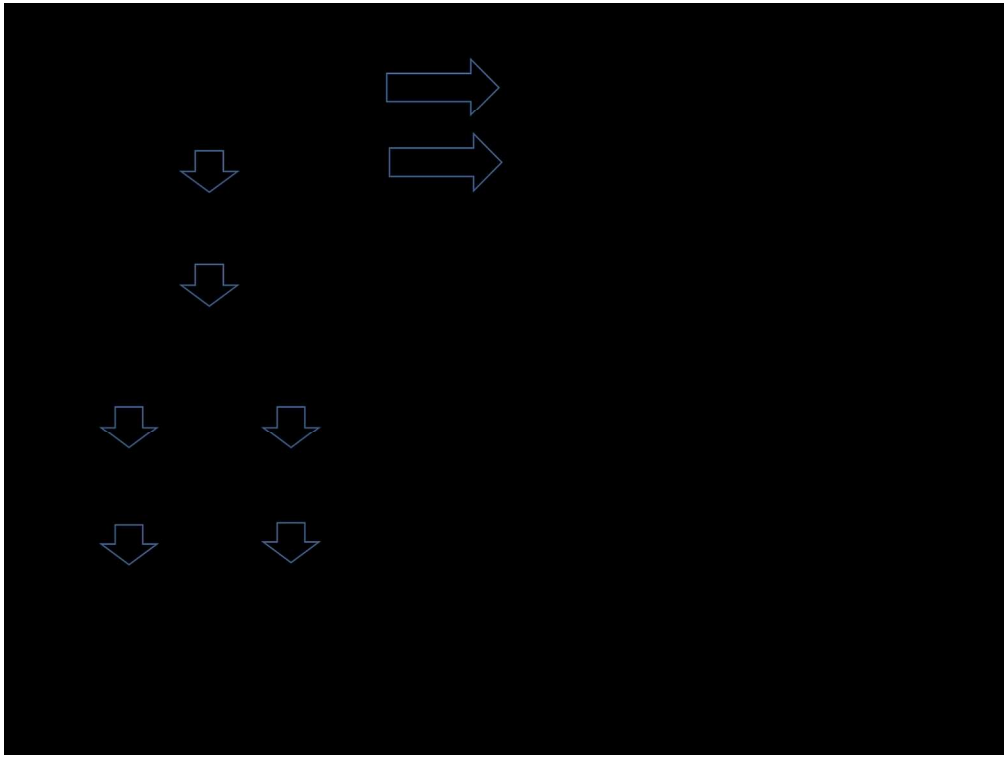


Figure 5. Flow chart of enrolled and ultimately randomised patients  
119x90mm (300 x 300 DPI)

ew only

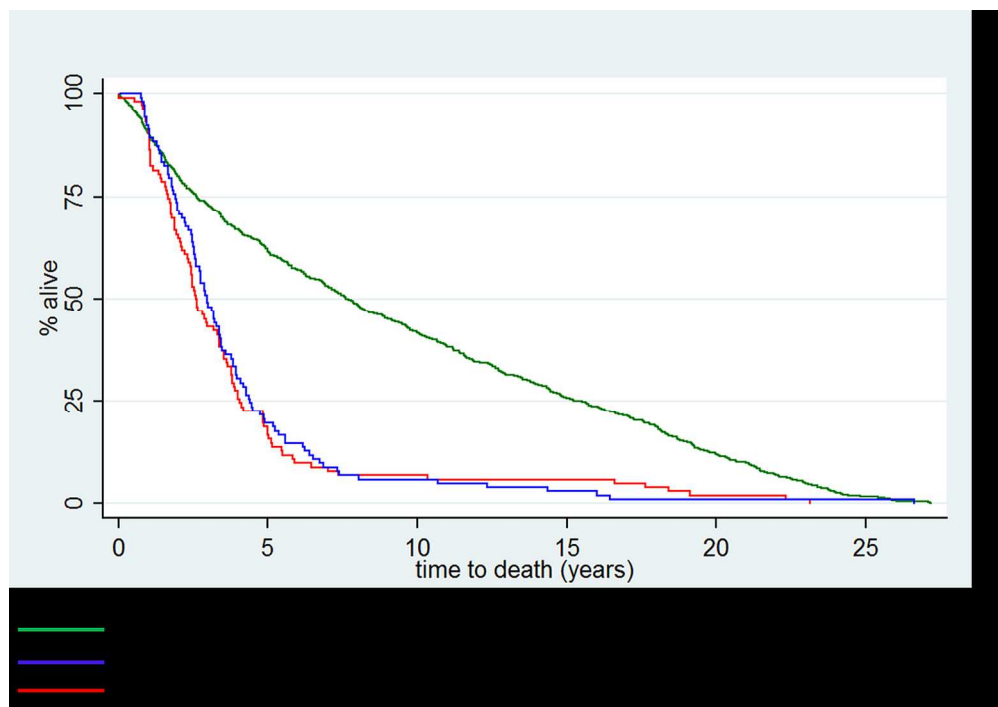


Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or 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
<b>Title and abstract</b>						
	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	
<b>Introduction</b>						
Background and objectives	2a	Scientific background and explanation of rationale	5-6	4-9	None written	
	2b	Specific objectives or hypotheses	3	2	2	
<b>Methods</b>						
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	This was of course implicit that these were in units performing colorectal cancer
					CEA assays	
					4	

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			
<b>Results</b>						
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.
<b>Discussion</b>						
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			
<b>Other information</b>						
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	

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2 \* 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  
3 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  
4 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  
5 other CONSORT extensions, e.g. for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. See  
6 [www.consort-statement.org](http://www.consort-statement.org) for more details.  
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For peer review only

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004385.R2
Article Type:	Research
Date Submitted by the Author:	08-Mar-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; Imperial College London, Cardiac Surgery Russell, Christopher; University College London, Surgery
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Colorectal surgery < SURGERY, Chemical pathology < PATHOLOGY, Adult oncology < ONCOLOGY, Adult gastroenterology < GASTROENTEROLOGY, CHEMICAL PATHOLOGY

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Manuscripts



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Title

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

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## 22 Abstract

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

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

28 Setting: 58 hospitals in the United Kingdom.

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

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

32 Primary outcome measure: survival.

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

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

41

42 International Standard Randomised Controlled Trial Number ISRCTN76694943

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44 Date applied 1<sup>st</sup> July 2001 and recorded as 'completed'

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2  
3 46 Strengths and limitations of this study  
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- 5 47 • The CEA Second-Look Trial was a well-planned and carefully executed study with a  
6 48 clear question and a well-defined outcome of interest.
- 7
- 8 49 • Second-look surgery prompted by the best available indicator of recurrence at the  
9 50 time conferred no survival advantage.
- 10
- 11 51 • A further strength, and a reason to publish this trial now, is that it shows that  
12 52 randomised trials in surgery can be done and that the result may be contrary to the  
13 53 beliefs and expectations of practitioners based on their uncontrolled observations.
- 14

15 54 A limitation is that present day means of non-invasive detection of asymptomatic recurrence  
16 55 were not available at the time of the CEA Second-Look Trial. A recently reported  
17 56 randomised controlled trial (FACS) in which regular CEA and/or CT monitoring were  
18 57 compared with minimum follow-up showed no survival advantage associated with earlier  
19 58 detection through monitoring.  
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3 59 Introduction  
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6 60  
61 The Working Party of the Carcinoembryonic antigen (CEA) Second-Look Trial set the scene  
62 for their trial in their protocol in 1982(1) The principle finding, that CEA monitoring to  
63 detect asymptomatic recurrence was not associated with improved survival, was announced  
64 in a letter to the Journal of the American Medical Association in 1994 by Northover, the then  
65 Chief Investigator.(2) The writing of the trial for publication lapsed. We here report the trial  
66 under the RIAT initiative (Restoring invisible and abandoned trials).(3;4)  
67

68 It had been observed during the 1970s that the outlook for patients with colorectal cancer was  
69 not good. Only one in four patients survived for five years after diagnosis and radical surgery  
70 was observed to be curative in under half of patients (5). Results had not improved in several  
71 decades.(1;6;7). Refinements in primary operative techniques had not made a difference(8)  
72 and it was considered unlikely that technical modifications would lead to improvement in  
73 survival following surgery.(5;6) Routine surgical follow-up had not led to further surgery  
74 being shown to be beneficial: clinical evidence of recurrence usually meant that the tumour  
75 would be unresectable at second-look laparotomy.(9) The published experience of members  
76 of the Working Party who developed and launched the trial was that of 180 patients, followed  
77 up from six months to 15 years, with a total of 2319 out-patient clinic visits, only one patient  
78 could be considered to have had a potentially curative second-look operation.(10) They  
79 concluded that to re-resect with prospect of benefit, recurrence had to be detected before it  
80 was clinically evident(1) but more pro-active clinical follow-up of asymptomatic patients by  
81 three monthly sigmoidoscopy, barium enema and chest X-ray (the methods available at the  
82 time) had failed to show improvement in 5-year survival.(11) Nevertheless, there had been  
83 several reports of 30% five-year survival in selected patients after radical resection of  
84 recurrent cancer(7;12;13) and resection was believed to sometimes lead to “cure”.(7;12-14)  
85

86 *Improving detection and treatment of recurrent disease: the context in 1982*  
87

88 The trial development group considered the evidence available at the time for methods of  
89 detecting recurrence early and a founding principle of the CEA Second-Look Trial was that  
90 early detection of recurrent tumour would only be justifiable if further treatment offered the  
91 prospect of benefit to the individual patient.(1) The evidence available to the trial working  
92 party in 1982 is outlined below.  
93

94 Figure 1 Working Party membership  
95

96 *The Wangensteen Approach:*

97 During the 1950s the systematic use of a policy-based second operation was reported.  
98 Patients at high risk of recurrence (those with Dukes' Stage C tumours) were re-operated on  
99 at 6-monthly intervals, resecting recurrence when found, until they were ‘tumour free’. If  
100 cancer had been found the patients were scheduled for 3<sup>rd</sup> and more “looks”, up to six further  
101 abdominal operations, “before the abdomen was free of cancer”. Once a patient had  
102 undergone a negative laparotomy, no more surgery was recommended. Sixty-four patients  
103 with colon or rectal cancer were managed in this way. In 35 (55%) of them the “second-  
104 look” laparotomy was negative for the discovery of recurrent cancer, seven of whom  
105 subsequently had clinical recurrence. There were four (6%) operative deaths.(15) The  
106 Working Party concluded that this ‘blanket second-look’ policy might have produced some  
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3 107 “cures” but entailed high rates of negative laparotomy and an unacceptable operative  
4 108 mortality rate.(1)

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6 110

7 111 Figure 2 from Wangensteen 1954

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10 114 *The CEA-prompted Second-Look Approach*

11 115 CEA had been shown to detect recurrence of colorectal cancer following surgery.(16-21)

12 116 CEA rose, on average, four months prior to clinical evidence of recurrence(17) and there

13 117 were reports of the use of serial serum carcinoembryonic antigen (CEA) assays to detect

14 118 asymptomatic recurrences in the belief that curative resection would be possible more

15 119 frequently.(16-18) Several groups used CEA in this way, and found low false positive

16 120 rates(9;22) and the resectability rate of the recurrence was higher than when clinical criteria

17 121 were used to prompt re-operation.(9) In the largest published experience of CEA in a post-

18 122 operative monitoring role(9;16) recurrent tumour, which was resectable, was found in 70% in

19 123 whom re-operation was prompted by a rise in the serum CEA compared with a quarter of

20 124 patients undergoing second-look laparotomy prompted by clinical indications. Others had

21 125 not found CEA to be useful in this post-operative monitoring role. Even if efficacy of CEA

22 126 detected recurrence was accepted, there was still the unresolved question of effectiveness: if

23 127 more patients were detected and there were more instances of resectable recurrence, did that

24 128 lead to better survival and patient benefit? The conflicting interpretations of observational

25 129 data resulted in calls for trials(16;22;23) including one within a 1981 NIH Consensus

26 130 Statement.(21)

27 131

28 132

29 133 The objective of the CEA Second-Look Surgery Trial was to determine whether, following

30 134 potentially curative primary surgery for colorectal cancer, mortality could be decreased by a

31 135 policy of second-look surgery prompted by rising serum carcinoembryonic antigen (CEA).

32 136 The trial ran from 1982 to 1993. The main result, that there was no survival advantage, was

33 137 reported in 1994 to the British Oncological Association(24) and was published in a letter to

34 138 the Journal of the American Medical Association.(2)

35 139

36 140 Detection and reoperation for asymptomatic colorectal cancer recurrence has since become

37 141 routine both in the form of hepatic resection(25) and pulmonary metastasectomy(26) but

38 142 without evidence from controlled trials for either practice.(27;28) When doubts were raised

39 143 about the security of the evidence in the British Medical Journal in 2007(27) a general belief

40 144 existed that randomised controlled trials of the effectiveness of resection of liver or lung

41 145 metastases were not possible and were not needed. These paired beliefs are brought into

42 146 question by the previously unpublished CEA Second-Look Trial: a randomised trial had been

43 147 done and the presumed benefit of surgery for cancer recurrence was not seen.(2;24)

44 148

45 149 *Closure of the trial in 1993 and gaining access to the data in 2011*

46 150 The RIAT restorative authors had been involved in various studies related to surgery for

47 151 disseminated colorectal cancer(27;29;30) including a conundrum as to whether discovery of

48 152 an elevated CEA assay should prompt, or be considered a contra-indication to, pulmonary

49 153 metastasectomy.(31) We knew the CEA trial had been recruiting in the 1980s but when we

50 154 searched the literature for the result of the trial found nothing later than 1994.(2;24) In 2009

51 155 we contacted the chief investigator of the trial at the time of its closure (JMAN) and the

52 156 present director of the University College London Cancer Trials Centre (JAL). We were

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3 157 informed that the data were irretrievably lost. However, staff at UCL CTC were aware that  
4 158 CEA trial data were still in the department and after further enquiries RCGR gained access to  
5 159 anonymised electronic data in 2011. The process of data restoration is described later. It was  
6 160 agreed that the trial would be published as part of 'Restoring invisible and abandoned  
7 161 trials'(RIAT).(3;4)  
8 162

9 163 Amongst the documents made available to the RIAT restorative authors were listed the  
10 164 members of the trial development group in the 1982 protocol(1) and the contributors to the  
11 165 1994 manuscript.(32) None of these individuals expressed an interest in resuming work on  
12 166 the trial or were in a position to do so. When we contacted them later to share the restored  
13 167 data with them no one raised any objection but on the contrary encouraged us to publish their  
14 168 findings.  
15 169

16 170  
17 171  
18 172 Methods: trial intent and design

19 173 *The recruitment intentions and the trial protocol as presented here are essentially as written*  
20 174 *in the manuscript prepared in 1994 with the full intention of publishing the trial.(32) The text*  
21 175 *has been edited by the RIAT authors but no new material has been introduced.*  
22 176

23 177 The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years  
24 178 and to follow them for five years. The study was specifically designed with late  
25 179 randomisation in order to maximise statistical power. It was originally intended to recruit  
26 180 2,000 patients with the anticipation that about 25% would show a CEA rise as the first  
27 181 evidence of possible recurrence. This number would have provided 95% power to detect an  
28 182 improvement in two year survival from the second-look procedure from 25% to 55% at  
29 183  $\alpha=0.05$ . The protocol stated that for the trial to be stopped prematurely very stringent levels  
30 184 of significance ( $p<0.001$ ) would be used. Analyses of the randomised groups were to be by  
31 185 Kaplan-Meier lifetables and the logrank test on 'intention to treat'.(32)  
32 186

33 187 Their intentions were explicitly set out as follows in 1981:(33)

34 188 *'So far as society in general is concerned, if CEA monitoring is shown to be of benefit in this*  
35 189 *study, then it will be a powerful incentive to the great majority of surgeons who see no*  
36 190 *obvious advantage in routine CEA monitoring to adopt the technique; as colorectal cancer is*  
37 191 *the second commonest killing cancer in the Western world, the benefits would thus be*  
38 192 *enormous. If, however, CEA monitoring is shown to be of no long term therapeutic value*  
39 193 *then it should cease to be used in its presently available form, and patients will thereby be*  
40 194 *spared the 'needless anxiety' of premature knowledge of their impending death.(23)'*  
41 195

42 196 The CEA trial design was devised so that clinical follow-up would remain unbiased, and  
43 197 allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent  
44 198 colorectal cancer. After potentially curative surgery for colorectal cancer, all eligible patients  
45 199 were to be monitored identically using conventional clinical follow-up together with regular  
46 200 CEA assay, performed centrally. Clinicians would not be informed of the result. When a  
47 201 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into  
48 202 either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm,  
49 203 the clinician would immediately be informed of the CEA rise so that the patient could be  
50 204 urgently screened to exclude widespread metastatic disease or a non-malignant cause for the  
51 205 CEA rise. If neither was found, and the patient was medically fit for operation, the protocol  
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3 206 required second-look surgery to locate and remove any treatable recurrence. In the case of  
4 207 patients in the 'Conventional' arm, the clinician would not be informed of the 'significant'  
5 208 CEA rise nor of the fact that they had been randomised to not have the CEA rise revealed.  
6 209

7 210 The primary outcome was survival based on death certification through the Office of  
8 211 Population Censuses and Surveys (OPCS) (now called the Office for National Statistics  
9 212 (ONS)). No subset analyses were planned.  
10 213

11 214 The intention as stated in the protocol was that the trial would produce:  
12 215

- 13 216 a) a definitive answer concerning the effectiveness of CEA-prompted second-look  
14 217 surgery to improve survival  
15 218 b) an accurate picture of the 'lead time' produced by CEA compared to clinically  
16 219 indicated second-look surgery  
17 220 c) further data relating CEA levels to tumour histology and topography, and  
18 221 d) a large data base on the natural history of colorectal cancer.(1)  
19 222

20 223 The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements  
21 224 give no indication as to the precise nature of analyses that might follow and are regarded as  
22 225 opportunities for explanatory subset analyses which were not in the event carried out.  
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230 Methods: the conduct of the trial 1982 to 1993

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

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236

#### 237 *Selection of patients*

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

246

247

#### 248 *Management of the primary tumour*

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

257

#### 258 *Consent*

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

263

#### 264 *Baseline data*

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

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277 Figure 3: Trial flow diagram

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#### 279 *Monitoring of Patients*

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3 280 Clinical follow-up of all patients continued in an identical manner (three monthly for the first  
4 281 two years and six monthly for the next three years) whilst blood for CEA assay was drawn  
5 282 monthly for the first three years and three monthly for the next two years. If the patient  
6 283 remained well and the CEA was within normal limits as defined by a pre-tested algorithm,  
7 284 monitoring continued according to the schedule.  
8  
9 285

#### 10 286 *CEA assay*

11 287 Ten mls of whole blood were taken from each patient. The serum was separated and sent to  
12 288 the Trials Centre in special plastic phials. After logging receipt, the samples were forwarded  
13 289 to the Medical Oncology Department at Charing Cross Hospital for assay. The results were  
14 290 returned to the Trials Centre for recording and action if appropriate. This centralised system  
15 291 ensured that all participating clinicians were kept blind to the CEA results for their patients.  
16 292 It also ensured quality control of the CEA assay as there was no possibility of inter-laboratory  
17 293 variation.  
18  
19 294

20 295 Serum CEA values were measured by double antibody radioimmunoassay.(34-36) A bank of  
21 296 serum samples has been retained at -20°C.  
22 297

#### 23 298 *Monitoring assay compliance pre-randomisation*

24 299 Throughout the trial, compliance with blood sampling was monitored by the secretariat.  
25 300 Clinicians were reminded each month of the patients for whom samples were due; those who  
26 301 had missed the previous visit were highlighted as urgent. The percentage compliance for  
27 302 each participating patient was calculated as the number of samples received divided by those  
28 303 expected x 100. The median time between samples was also calculated. Failure to achieve  
29 304 50% of the expected samples was defined as poor compliance. Since the sensitivity to detect  
30 305 CEA rises in such patients was greatly reduced they were excluded from randomisation.  
31  
32 306

#### 33 307 34 308 *'Significant' Rises in CEA*

35 309 A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on  
36 310 two successive occasions and one of the following conditions was also met: the CEA level  
37 311 was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the  
38 312 highest value was more than 7ng/ml above the lowest value ever recorded. If a 'significant'  
39 313 rise in CEA occurred, the record of the patient was reviewed at the Trials Centre and  
40 314 provided no evidence of suspected colorectal or other disease was recorded in the CRF, the  
41 315 patient was randomised either into an 'Aggressive' or 'Conventional' arm.  
42  
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#### 44 317 Figure 4: CEA algorithm

#### 45 318 46 319 *Randomisation*

47 320 Patients were randomised equally between the two arms (1:1). Patients whose compliance  
48 321 was between 50 and 70% or whose immediate post-operative sample had not been received  
49 322 within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was  
50 323 also stratified by participating clinician. A block size of two was used in order to maintain as  
51 324 close a balance as possible between the two treatment arms.  
52  
53 325

54 326 If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise  
55 327 immediately by telephone from the trial centre and subsequently in writing and was requested  
56 328 to contact the patient urgently. Patients were informed of their situation including the fact  
57 329 that they had been randomised within the trial to undergo a second-look procedure. This was  
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3 330 then undertaken if the patient gave written informed consent. The surgeon carried out a full  
4 331 clinical work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g.,  
5 332 change in smoking or drinking habit) and to identify any incurable distant spread. In the  
6 333 absence of these conditions the surgeon undertook a mini-laparotomy, proceeding to full  
7 334 laparotomy with macroscopic clearance of disease, should this be possible.

8  
9 335 For patients randomised to the 'Conventional' arm no further action was taken; the clinician  
10 336 was neither informed that the CEA had risen nor that the patient had been randomised.

11 337

12 338 If at any stage a patient in the study developed clinical evidence of recurrent disease the  
13 339 clinician was at liberty to manage the patient according to usual practice. If the disease was  
14 340 in the abdomen and was thought to be treatable by a second-look operation with re-resection,  
15 341 this was acceptable. By the nature of the trial design, the clinician was blind as to whether  
16 342 such patients had been randomised to the 'Conventional' arm of the trial or had not been  
17 343 randomised because the CEA had failed to denote the presence of recurrent disease.

18 344

#### 19 345 *Second-Look Laparotomy*

20 346 The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate  
21 347 any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was  
22 348 detected all that was required prior to closure, was biopsy. Otherwise following a full  
23 349 excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the  
24 350 small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis  
25 351 was undertaken. The liver was fully mobilised to determine whether any tumour was present.  
26 352 Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then  
27 353 carried out with the objective of total extirpation of all recurrence. Complete data recording  
28 354 of the procedure along with the results of the histology of all potentially involved sites was  
29 355 required by the trial's office.

30 356

31 357 For patients in whom a radical resection was achieved after second-look surgery (motivated  
32 358 either on clinical information or because the patient had been randomised to the 'Aggressive'  
33 359 arm) the follow-up schedules for clinical examination and blood sampling reverted to those  
34 360 following the primary operation. However, for patients randomised to the 'Aggressive' arm,  
35 361 clinicians were immediately notified of any further CEA levels above 10ng/ml.

36 362

#### 37 363 *Death*

38 364 Every patient registered onto the study was 'flagged' with the Office of Population Censuses  
39 365 and Surveys (now ONS) who provide automatic notification of date of death. This enabled  
40 366 the trial centre to receive certified cause of death for all patients.

41 367

42 368

#### 43 369 *Trial oversight*

44 370 A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not  
45 371 entering patients into the trial was asked to review the data after the first 100 patients had  
46 372 been randomised, which occurred in January 1988, and again after 200 patients had been  
47 373 randomised in February 1993. At this point it was recommended by the Data Monitoring  
48 374 Committee that the trial stopped since it was very unlikely that any clinically important  
49 375 advantage would be demonstrated for patients undergoing second-look surgery.

50 376

51 377 Methods of the RIAT process

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#### 53 379 *The data*

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3 380 The RIAT restorative authors had been warned by the statisticians called in to look at the data  
4 381 in 2003-4 that “the databases were corrupted with key variables no longer  
5 382 abstractable”.(37;38) We found that the data on paper and on file were accessible and we had  
6 383 no reason to doubt the veracity of individual items. We found that the electronic files had  
7 384 numerous problems with formatting which made the files on the 1447 individual patients  
8 385 difficult to handle but that the data entries were not themselves corrupted.  
9 386

10 387 One of the RIAT restorative authors (KM) had worked in the trials units during the time the  
11 388 CEA Trial data were being accrued and knew the systems in use and their changes but was  
12 389 not directly involved in this trial at any stage.  
13 390

14 391 The questions raised and the problems encountered, were resolved as follows:  
15 392

- 16 393 • The codes indicating that a patient had met the criteria for CEA elevation and  
17 394 whether they were randomised to ‘active’ or ‘Conventional’ arm were preserved and  
18 395 tallied with the number in the 1994 manuscript.(32)  
19 396
- 20 397 • There were variations in the way dates were recorded in the database. There had been  
21 398 migrations of data from a ‘Prime’ server using ‘Universe’ to ‘Excel’ and the  
22 399 interpretation of the present authors, with information from contemporary witnesses  
23 400 was that in undertaking the task operators did not always correctly specify these data  
24 401 as ‘dates’ when importing, and/or allowed them to be converted to American date  
25 402 formats. These errors prevented calculations and would have defeated running a  
26 403 survival analysis without correction of the file entries. The dates were however  
27 404 visually readable and not ‘corrupt’. Some could be corrected by running current  
28 405 versions of software. Others were manually corrected by re-entering them in a  
29 406 Microsoft date format. Paper records were available to resolve uncertainties.  
30 407
- 31 408 • The next problem was in linking these three groups of patients (randomised to  
32 409 ‘Aggressive’, randomised to ‘Conventional’ and not randomised) to the dates for  
33 410 survival analysis. Individual patients were uniquely identified in the files by seven  
34 411 digit strings to which letters had been added at the beginning and end, possibly for  
35 412 trial administrators’ checklists or subgroup identification. Once we had established  
36 413 that the initial and terminal letters were redundant for analysis of the primary  
37 414 endpoint, we were able to write code to restore the seven digit strings.  
38 415
- 39 416 • It was evident that the seven digits did not represent a simple sequence but certain  
40 417 positions identified particular characteristics, such as participating centre. We  
41 418 recognised a consistent pattern of mismatch in the fourth digit, a zero in one file was  
42 419 an 8 in the other with all other digits remaining the same. It was suggested to us that  
43 420 the fourth digit replacement was used to identify patients suitable for *post hoc*  
44 421 subgroup analyses but no documentation was found to confirm this. By checking  
45 422 back to the dates of birth we were able to confirm that this systematic correction  
46 423 resolved the problem and most of the data were then usable.  
47 424
- 48 425 • By ranking all the data in the paired files for line by line visual inspection residual  
49 426 discrepancies were identified. Scrutinising the digit strings allowed for seven of the  
50 427 remaining eight pairs to be reconciled and verified on dates of birth. We failed to  
51 428 resolve only one out of 1447 records in each file. This patient had not been  
52 429 randomised.  
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4 431 • Inspection of the accrual of death dates was discontinuous for a couple of years  
5 432 suggesting a lapse in either recovery or entry. The current trials centre obtained  
6 433 permission to re-run the Office for National Statistics (ONS) search in July 2012.  
7 434

8 435 In summary, we identified several problems but they were systematic and not random (we  
9 436 would not use the value laden word 'corrupted'). We were able to rectify the formatting  
10 437 errors and verify that the data used for our analysis were correct. The Kaplan Meier analysis  
11 438 was re-run.  
12 439

## 13 440 14 441 Results 15 442

### 16 443 *The original main results 1994*

17 444 The study opened to recruitment in November 1982 and was closed by the Working Party, on  
18 445 the acceptance of a recommendation from the Data Monitoring Sub-committee, on 17th  
19 446 February 1993. During this period 1,447 patients were registered by 73 participating  
20 447 clinicians in 58 hospitals in the United Kingdom. Of these 39 (2.7%) were deemed ineligible  
21 448 since their CEA did not fall below 10 ng/ml by six weeks after surgery. A further 173 patients  
22 449 were excluded from analysis; four did not have a confirmed diagnosis of adenocarcinoma, 6  
23 450 were considered unfit for continued monitoring, 4 had a previous and 1 a simultaneous non-  
24 451 colorectal malignancy, 2 had metastatic disease, and 156 (10.8%) never complied with the  
25 452 requirement for monthly blood sampling or only did so for 3 months or less.  
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### 29 453 Figure 5 paper records of the CEA results

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31 454 Of 1,235 patients who continued in the trial, 80% achieved a greater than 60% compliance  
32 455 with blood sampling, whilst 12.5% registered between 40-59% of the required samples and  
33 456 only 7.5% had compliance of less than 40%. The majority of randomisations (160/216; 74%)  
34 457 were prior to the second anniversary of the primary diagnosis. Three patients randomised  
35 458 had prior recurrent (2) or metachronous (1) disease detected clinically, without a rise in CEA  
36 459 and were operated upon.  
37 460

38 461 Two hundred and sixteen patients developed a 'significant' rise in CEA and as no recurrent  
39 462 disease had been recorded at their latest trial follow-up, they were randomised by the Trial  
40 463 Office (108 to each arm). The median time from primary surgery to randomisation was 403  
41 464 days, (range 103 to 1754) with no statistical difference between the two groups.(32)  
42 465 The characteristics of patients in the two groups are given in Table 1.  
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479 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 <sup>1</sup>	36 (33.3)	38 (35.2)
Dukes' C <sup>2</sup>	17 (15.7)	10 ( 9.3)
Missing	4 ( 3.7)	6 ( 5.6)

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481

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

484

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

493

#### 494 *RIAT restoration and updated survival analysis*

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

498

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

503

504 Certification of death was obtained from ONS on behalf of the RIAT restorative authors for  
505 204 of 216 randomised patients who died between 17/10/1983 and 08/09/2011. There were  
506 equal numbers of patients in the two arms (108) and equal numbers of death dates were  
507 retrieved (102). We also have dates of death in 862 of the 1230 patients who were not  
508 randomised. Kaplan Meier analysis in these three groups is shown in Figure 6, showing  
509 survival of the 1230 participants who entered the trial but were not randomised and the 108  
510 participants randomised into each arm.

511

#### 512 Figure 6 Kaplan Meier analysis

513

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

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3 518 regarded as unlikely, therefore, that the lead time would decrease as further events occur. The  
4 519 analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12  
5 520 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs  
6 521 44% and 97% vs 70% at a year. The RIAT authors did not repeat this analysis.  
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10 525 Discussion

11 526 We have restored data sufficient to achieve the primary outcome of interest as specified by  
12 527 the CEA trialists:

13 528 “Does a policy of CEA-prompted second-look surgery following ‘curative’ resection  
14 529 of colorectal cancer produce a decrease in morbidity and mortality due to tumour  
15 530 recurrence, despite sequelae of second look surgery?”  
16 531

17 532

18 533 The answer is that acting on CEA elevation by second-look surgery did not reduce mortality  
19 534 compared with patients in whom similar CEA elevation remained unknown. This negative  
20 535 finding led to the closing of the trial in 1994(2;24) and we confirm it here. There was small  
21 536 non-significant excess of deaths in the ‘Aggressive’ arm. The burden of morbidity  
22 537 attributable to the greater number of investigations and operations was not captured by the  
23 538 trial protocol nor indeed the ‘needless anxiety’ which concerned Moertel(23) and the authors  
24 539 of the CEA trial protocol.(1)  
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27 542 The second planned analysis was to obtain an accurate picture of the ‘lead time’ produced by  
28 543 CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up  
29 544 patients considerably sooner than the clinical methods available at the time by 11 months  
30 545 (95% CI 7-14 months).  
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33 548 CEA monitoring for the purpose of early detection of asymptomatic cancer is currently  
34 549 recommended at least every 6 months in the first three years. In addition a minimum of two  
35 550 CT scans are recommended in the first three years.(39) The FACS trial, recently reported,  
36 551 has also shown no survival advantage from CEA monitoring compared with minimum  
37 552 follow-up.(40) More operations were performed with ‘curative intent’ for recurrent cancer in  
38 553 those having more intensive monitoring and there were more deaths (18.2%[164/901] vs  
39 554 15.9% [48/301]; difference, 2.3%; 95%CI, -2.6%to 7.1%). These results are similar to the  
40 555 findings in the CEA trial. Although the phrase ‘curative intent’ occurs about 40 times in the  
41 556 manuscript, better survival was not achieved with any of the three monitoring schedules  
42 557 compared with minimum follow-up.  
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46 561 The third and fourth intentions set out by the CEA trialists were c) to obtain further data  
47 562 relating CEA levels to tumour histology and topography and d) a large data base on the  
48 563 natural history of colorectal cancer. Multiple CEA assay results exist in the data we hold for  
49 564 1446 patients and it would be possible to link these to survival as a result of the RIAT  
50 565 restorative work.  
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53 568 With respect to the natural history of colorectal cancer although we trust the death  
54 569 certification data for the date of death it has been shown that “at least a third of all death  
55 570 certificates are likely to be incorrect”(41). No doubt aware of this and seeking much more  
56 571 detailed information, the CEA Trialists had asked for detailed post-mortem examinations. It  
57 572 appears that it was disagreement concerning explanatory analyses which contributed to the  
58 573 failure to publish the primary outcome of interest.(32) The purpose of such analyses would  
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3 568 be to discover subsets of patients in whom there was a benefit from the intervention under  
4 569 evaluation and to thus determine the characteristics of patients in whom the intervention  
5 570 might have had a beneficial effect by analysis of mediators and moderators.(42) There is a  
6 571 general objection to this exercise because it can lead to spurious associations.(43;44)  
7 572 Furthermore when there is no overall benefit found, as in the CEA Second-Look Trial, any  
8 573 subgroup(s) where there is a positive association between intervention and outcome must be  
9 574 balanced by one or more other groups where there was net harm. The methods section of the  
10 575 1994 manuscript states ‘Subgroup analyses have been performed to address specific issues  
11 576 but these need to be interpreted with appropriate caution.’(32) In the event no completed  
12 577 subset analyses were in the 1994 paper and the closing notes between the authors are on the  
13 578 matter of a subset analysis. We have not attempted any in restoring the trial.

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16 579  
17 580 The answer to the primary research question was clear in 1993 and was the explicit reason for  
18 581 stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery  
19 582 had been missed and in the absence of benefit there was net harm being done to the patients.  
20 583 The forms of second look surgery now widely practiced in colorectal cancer are liver and  
21 584 lung resection of metastases.

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- Full mobilisation of the liver at second-look laparotomy was included in the CEA  
25 587 Trial protocol. Hepatic resection has entered routine practice based on observational  
26 588 data(45) and an opportunity to do a randomised trial, for which a power calculation  
27 589 was proposed in 1992 from the Mayo Clinic(46) was not taken.(25)
- Two patients had a thoracotomy prompted by CEA elevation. Pulmonary  
28 590 metastasectomy for colorectal cancer is, after primary lung cancer, the second  
29 591 commonest thoracic cancer operation and is the subject of an ongoing randomised  
30 592 controlled trial.(47)

31 593  
32 594  
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34 595 The CEA Trial findings have been corroborated by the larger FACS trial. If the CEA trial  
35 596 results had been made available in 1994, and there is no evident reason why they should not  
36 597 have been, a more critical scrutiny of the evidence base that was used to bring liver and lung  
37 598 metastasectomy into practice. (25;30) might have been undertaken. The CEA Trial was a  
38 599 well-conceived and meticulously executed randomised trial and we hope that publishing it  
39 600 now more than twenty years after its completion will indicate the possibility of more  
40 601 randomised trials in surgery.(48)

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3 602 Legends

4 603

5 604 Figure 1. The “Working Party” that produced the protocol in 1982 for the CEA Second-Look  
6 605 Surgery trial.(1)

7 606

8 607 Figure 2. Illustration of operative findings in six successive operations seeking recurrence of  
9 608 colorectal cancer.(15)

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11 610 Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.(1)

12 611

13 612 Figure 4. Decision making algorithm for CEA to trigger second-look surgery.(15)

14 613

15 614 Figure 5. Flow chart of enrolled and ultimately randomised patients. ‘Blind’ in the bottom left  
16 615 box means that the clinical teams were unaware of the elevated CEA discovered and were  
17 616 unaware that the patients have been randomised. They were indistinguishable amongst the  
18 617 1230 non-randomised patients who were being followed-up. (See Figure 6)

19 618

20 619 Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446)  
21 620 following potentially curative colorectal cancer surgery. Patients who had CEA elevation  
22 621 according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA  
23 622 revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from  
24 623 Office for National Statistics in 104/108 in each arm. The green line is for all other patients.  
25 624 (N=862 of 1230) Some would have had clinically evident early recurrence precluding  
26 625 randomisation. The initial plateau is an illustration of a death free interval(49) or “immortal  
27 626 time bias”(50) Patients in prospective studies may have a built in obligatory survival time  
28 627 from some starting point in order to attain the requirements to be included in the data set.  
29 628 This is an artefact but may be absorbed into survival time adding to and not readily  
30 629 distinguished from survival time attributed to treatment.

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#### 28 668 Contributor statement

29 669 TT instigated the recovery of the data, worked on the database recovery described in the  
30 670 manuscript and wrote the first and edited the final version of the manuscript.

31 671 KM navigated the data files and worked on the database recovery described in the  
32 672 manuscript.

33 673 FF performed the analysis of the recovered data and the presentation of the analysis.

34 674 RCGR negotiated access to the data and with TT contacted and interviewed the members of  
35 675 the original trial team.

36 676 All authors have read and contributed to successive iterations of the manuscript and approve  
37 677 the submitted version.  
38 678

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40 680 Research Campaign and the National Institute of Health. The restoration of the trial was  
41 681 unfunded. The four RIAT restorative authors gave their time unpaid.  
42 682

#### 43 683 Data sharing

44 684 We are prepared to share the anonymised electronic data in our possession. The chief  
45 685 investigator (JMAN) and the chair of data monitoring committee (MB) provided a signed  
46 686 agreement on 21<sup>st</sup> February 2014 to allow access to the archived paper records and electronic  
47 687 files (held by UCLCTC) at the discretion of the RIAT authors. CEA Survival data for two  
48 688 randomised and one non randomised groups can be accessed in the Dryad data repository:  
49 689 doi:10.5061/dryad.s3p05  
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11 701 Trials Centre (CRC CTC) King's College Hospital Medical School, London and/or were  
12 702 listed as contributors in the 1994 manuscript from the CRC CTC at the Rayne Institute, 123  
13 703 Coldharbour Lane, London SE5 9NU: M Baum, RHJ Begent, H Ellis, J Houghton, M Irving,  
14 704 CA Lennon, JMA Northover, WW Slack and CB Wood. We are particularly grateful to  
15 705 JMAN who met with TT and RCGR at the Royal Society of Medicine in London on Monday  
16 706 10<sup>th</sup> February 2014 and read and commented on a near final version of the manuscript and  
17 707 agreed our interpretation of the trial results. The principle findings reported here corroborate  
18 708 those in his letter to JAMA in 1994. JMAN helped us understand the sequence of events  
19 709 leading to the closure of the trial and subsequent lapse in writing up the full report.

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24 711 None of the authors have conflicts of interest.

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2 Title

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

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19 | ~~ISRCTN76694943~~

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#### 45 Contributor statement

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

55  
 56  
 57 Funding. The CEA Second-Look Trial opened in 1982 and was jointly funded by Cancer  
 58 Research Campaign and the National Institute of Health. The restoration of the trial was  
 59 unfunded. The four RIAT restorative authors gave their time unpaid.

#### 60 Data sharing

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

#### 65 Acknowledgments

66  
 67 The RIAT authors are grateful to Jonathan Ledermann, Director of the Cancer Research UK  
 68 & UCL Cancer Trials Centre, University College London, (where the CEA files were stored)  
 69 and Sharon Forsyth for her assistance in accessing the CEA trial data and updating the Office  
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Comment [T1]: [Editor: we will send this written agreement.]



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7 71 | of National Statistics records for death registration. We acknowledge the assistance of Sonya  
8 72 | Crowe of UCL's Clinical Operational Research Unit is technical aspects of restoring the  
9 73 | electronic files to a usable state. The RIAT authors also met with the following persons who  
10 74 | were members of the 1982 Working Party at the Cancer Research Campaign Clinical Trials  
11 75 | Centre (CRC CTC) King's College Hospital Medical School, London and/or were listed as  
12 76 | contributors in the 1994 manuscript from the CRC CTC at the Rayne Institute, 123  
13 77 | Coldharbour Lane, London SE5 9NU: M Baum, RHJ Begent, H Ellis, J Houghton, M Irving,  
14 78 | CA Lennon, JMA Northover, WW Slack and CB Wood. ~~We are grateful to them for frank~~  
15 79 | ~~discussions concerning the progress of the study and the factors leading to its abandonment.~~  
16 80 | ~~We are particularly grateful to JMAN who met with TT and RCGR at the Royal Society of~~  
17 81 | ~~Medicine in London on Monday 10<sup>th</sup> February 2014 and read and commented on a near final~~  
18 82 | ~~version of the manuscript and agreed our interpretation of the trial results. The principle~~  
19 83 | ~~findings reported here corroborate those in his letter to JAMA in 1994. JMAN helped us~~  
20 84 | ~~understand the sequence of events leading to the closure of the trial and subsequent lapse in~~  
21 85 | ~~writing up the full report. We acknowledge the assistance of Sonya Crowe of UCL's Clinical~~  
22 86 | ~~Operational Research Unit is technical aspects of restoring the electronic files to a usable~~  
23 87 | ~~state.~~

24 88 | FF is partly funded by the British Heart Foundation.

25 89 | None of the authors have conflicts of interest.

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91  
92 Abstract

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

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

98 Setting: 58 hospitals in the United Kingdom and Europe.

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

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

102 Primary outcome measure: survival.

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

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

111  
112 -International Standard Randomised Controlled Trial Number  
113 ISRCTN76694943 Date applied 1<sup>st</sup> July 2001 and recorded as 'completed'

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7 115 Strengths and limitations of this study

- 8 116 • The CEA Second-Look Trial was a well-planned and carefully executed study with a  
9 117 clear question and a well-defined outcome of interest.
- 10 118 • Second-look surgery prompted by the best available indicator of recurrence at the  
11 119 time conferred no survival advantage.
- 12 120 • A further strength, and a reason to publish this trial now, is that it shows that  
13 121 randomised trials in surgery can be done and that the result may be contrary to the  
14 122 beliefs and expectations of practitioners based on their uncontrolled observations.

15 123 A limitation is that present day means of non-invasive detection of asymptomatic recurrence  
16 124 were not available at the time of the CEA Second-Look Trial. A recently reported  
17 125 randomised controlled trial (FACS) in which CEA and/or CT were compared with minimum  
18 126 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.]

127 Introduction

128  
129 The Working Party of the Carcinoembryonic antigen (CEA) Second-Look Trial set the scene  
130 for their trial in their protocol in 1982(1) The principle finding, that CEA monitoring to  
131 detect asymptomatic recurrence was not associated with improved survival, was announced  
132 in a letter to the Journal of the American Medical Association in 1994 by Northover, the then  
133 Chief Investigator.(2) The writing of the trial for publication lapsed. We here report the trial  
134 under the RIAT initiative (Restoring invisible and abandoned trials).(3;4)  
135

136 It ~~had been was~~ observed during the 1970s that the outlook for patients with colorectal cancer  
137 was not good. Only one in four patients survived for five years after diagnosis and radical  
138 surgery was observed to be curative in under half of patients (5)(4). Results had not improved  
139 in several decades.(1;6;7)(2-4). Refinements in primary operative techniques had not made a  
140 difference(8)(5) and it was considered unlikely that technical modifications would lead to  
141 improvement in survival following surgery.(5;6)(4;2) Routine surgical follow-up had not led  
142 to further surgery being shown to be beneficial: clinical evidence of recurrence usually meant  
143 that the tumour would be unresectable at second-look laparotomy.(9)(6) The published  
144 experience of members of the ~~Carcinoembryonic antigen (CEA) Second Look Trial Working~~  
145 ~~Party who developed and launched the trial development group~~ was that of 180 patients,  
146 followed up from six months to 15 years, with a total of 2319 out-patient clinic visits, only  
147 one patient could be considered to have had a potentially curative second-look  
148 operation.(10)(7) ~~They concluded that to~~ re-resect with prospect of benefit, recurrence had to  
149 be detected before it was clinically evident(1)(4) but more pro-active clinical follow-up of  
150 asymptomatic patients by three monthly sigmoidoscopy, barium enema and chest X-ray (the  
151 methods available at the time) had failed to show improvement in 5-year survival.(11)(8)  
152 Nevertheless, there had been several reports of 30% five-year survival in selected patients  
153 after radical resection of recurrent cancer(7;12;13)(3;9;10) and resection was believed to  
154 sometimes lead to “cure”.(7;12-14)(3;9-11)  
155

156 *Improving detection and treatment of recurrent disease: the context in 1982*

157  
158 The trial development group considered the evidence available at the time for methods of  
159 detecting recurrence early and a founding principle of the CEA Second-Look Trial was that  
160 early detection of recurrent tumour would only be justifiable if further treatment offered the  
161 prospect of benefit to the individual patient.(1)(4) The evidence available to the trial working  
162 party in 1982 is outlined below.

163  
164 Figure 1 Working Party membership

165  
166 *The Wangenstein Approach:*

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

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176 | ~~CEA-Working Party trialists~~ concluded that this ‘blanket second-look’ policy might have  
 177 | produced some “cures” but entailed high rates of negative laparotomy and an unacceptable  
 178 | operative mortality rate. ~~(1)(4)~~

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181 | Figure 2 from Wangenstein 1954

#### 184 | *The CEA-prompted Second-Look Approach*

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

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

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

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#### 220 | *Closure of the trial in 1993 and gaining access to the data in 2011*

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

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7 226 | found nothing later than 1994. ~~(2;24)(21;22)~~ In 2009 we contacted the chief investigator of the  
8 227 | trial at the time of its closure (JMAN) and the present director of the University College  
9 228 | London Cancer Trials Centre (JAL). We were informed that the data were irretrievably lost.  
10 229 | However, staff at UCL CTC were aware that CEA trial data were still in the department and  
11 230 | after further enquiries RCGR ~~the RIAT authors~~ gained access to anonymised electronic data  
12 231 | in 2011. The process of data restoration is described later. It was agreed that the trial would  
13 232 | be published as part of 'Restoring invisible and abandoned trials'(RIAT).(3;4)  
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15 234 | Amongst the documents made available to the RIAT restorative authors were listed the  
16 235 | members of the trial development group in the 1982 protocol ~~(1)(4)~~ and the contributors to the  
17 236 | 1994 manuscript. ~~(32)(30)~~ None of these individuals expressed an interest in resuming work  
18 237 | on the trial or were in a position to do so. When we contacted them later to share the restored  
19 238 | data with them no one raised any objection but on the contrary encouraged us to publish their  
20 239 | findings.  
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25 244 | Methods: trial intent and design

26 245 | *The recruitment intentions and the trial protocol as presented here are essentially as written*  
27 246 | *in the manuscript prepared in 1994 with the full intention of publishing the trial. ~~(32)(30)~~ The*  
28 247 | *text has been edited by the RIAT authors but no new material has been introduced.*

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29 248 | The CEA Second-Look Trial was intended to recruit at least 2000 patients over three years  
30 249 | and to follow them for five years. The study was specifically designed with late  
31 250 | randomisation in order to maximise statistical power. It was originally intended to recruit  
32 251 | 2,000 patients with the anticipation that about 25% would show a CEA rise as the first  
33 252 | evidence of possible recurrence. This number would have provided 95% power to detect an  
34 253 | improvement in two year survival from the second-look procedure from 25% to 55% at  
35 254 |  $\alpha=0.05$ . The protocol stated that for the trial to be stopped prematurely very stringent levels  
36 255 | of significance ( $p<0.001$ ) would be used. Analyses of the randomised groups were to be by  
37 256 | Kaplan-Meier lifetables and the logrank test on 'intention to treat'.(32)

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38 257 |  
39 258 | Their intentions were explicitly set out as follows in 1981: ~~(33)(31)~~

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40 259 | *'So far as society in general is concerned, if CEA monitoring is shown to be of benefit in this*  
41 260 | *study, then it will be a powerful incentive to the great majority of surgeons who see no*  
42 261 | *obvious advantage in routine CEA monitoring to adopt the technique; as colorectal cancer is*  
43 262 | *the second commonest killing cancer in the Western world, the benefits would thus be*  
44 263 | *enormous. If, however, CEA monitoring is shown to be of no long term therapeutic value*  
45 264 | *then it should cease to be used in its presently available form, and patients will thereby be*  
46 265 | *spared the 'needless anxiety' of premature knowledge of their impending death. ~~(23)(20)~~*  
47 266 |  
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49 268 | The CEA trial design was devised so that clinical follow-up would remain unbiased, and  
50 269 | allow specific evaluation of the role of CEA-indicated surgery in the treatment of recurrent  
51 270 | colorectal cancer. After potentially curative surgery for colorectal cancer, all eligible patients  
52 271 | were to be monitored identically using conventional clinical follow-up together with regular  
53 272 | CEA assay, performed centrally. Clinicians would not be informed of the result. When a  
54 273 | 'significant' CEA rise was recorded, patients were to be randomised by the Trials Centre into  
55 274 | either 'Aggressive' or 'Conventional' arms. In the case of patients in the 'Aggressive' arm,



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7 275 the clinician would immediately be informed of the CEA rise so that the patient could be  
8 276 urgently screened to exclude widespread metastatic disease or a non-malignant cause for the  
9 277 CEA rise. If neither was found, and the patient was medically fit for operation, the protocol  
10 278 required second-look surgery to locate and remove any treatable recurrence. In the case of  
11 279 patients in the 'Conventional' arm, the clinician would not be informed of the 'significant'  
12 280 CEA rise nor of the fact that they had been randomised to not have the CEA rise revealed.  
13 281

14 282 The primary outcome was survival based on death certification through the Office of  
15 283 Population Censuses and Surveys (OPCS) (now called the Office for National Statistics  
16 284 (ONS)). No subset analyses were planned.  
17 285

18 286 The intention as stated in the protocol was that the trial would produce:  
19 287

- 20 288 a) a definitive answer concerning the effectiveness of CEA-prompted second-look  
21 289 surgery to improve survival  
22 290 b) an accurate picture of the 'lead time' produced by CEA compared to clinically  
23 291 indicated second-look surgery  
24 292 c) further data relating CEA levels to tumour histology and topography, and  
25 293 d) a large data base on the natural history of colorectal cancer. (1)(4)

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26 294  
27 295 The RIAT restorative authors regard a) and b) as planned analyses. The c) and d) statements  
28 296 give no indication as to the precise nature of analyses that might follow and are regarded as  
29 297 opportunities for explanatory subset analyses which were not in the event carried out.  
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7 302 Methods: the conduct of the trial 1982 to 1993

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9 304 The trial was coordinated (initially) from the Cancer Research Campaign (CRC) Clinical  
10 305 Trials Centre at King's College Hospital. CEA assays were performed using a  
11 306 radioimmunoassay technique at a single centre at Charing Cross Hospital.  
12 307

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#### 15 310 *Selection of patients*

16 311 All patients up to the age of 76 who had undergone a potentially curative resection for  
17 312 adenocarcinoma of the colon or rectum and who were fit and willing to adhere to the post-  
18 313 operative monitoring routine were eligible for the study. Patients were excluded if there was  
19 314 evidence of incurable distant spread, either pre-operatively or during the primary operation,  
20 315 or if the CEA level failed to return to the normal range (<10 ng/ml) within six weeks of  
21 316 primary surgery. Patients who had previously received treatment for other types of cancer,  
22 317 apart from basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix  
23 318 adequately cone biopsied, were excluded from the study.  
24 319

#### 25 320 *Management of the primary tumour*

26 321 A pre-operative blood sample for CEA assay was taken from all patients with suspected  
27 322 colorectal adenocarcinoma who otherwise fulfilled the trial entry criteria. This was a  
28 323 pragmatically designed study so surgeons were at liberty to use their normal operative  
29 324 technique and to employ pre- or post-operative radiotherapy or adjuvant chemotherapy as  
30 325 was seen fit, however they were asked to remain consistent regarding the treatment used for  
31 326 any particular type of disease. If at laparotomy, a potentially curative resection was  
32 327 performed and subsequent histology confirmed the diagnosis of adenocarcinoma, the patient  
33 328 was given a full explanation of the study and could be registered.  
34 329

#### 35 330 *Consent*

36 331 The 1982 protocol includes a consent form (Consent form ~~1A~~) to be completed at registration  
37 332 and a further form (Consent form ~~2B~~) for patients who were randomised to a 'Second-Look  
38 333 Laparotomy'. ~~There was a -and-a-~~ protocol amendment in which the word 'cancer' is to be  
39 334 replaced throughout by 'a growth'. (1)(4)  
40 335

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#### 41 336 *Baseline data*

42 337 The surgeon carried out investigations to detect the presence of synchronous colorectal  
43 338 tumours (both benign and malignant) and to exclude occult liver spread; (usually barium  
44 339 enema examination and ultrasound or CT scan of the liver). In addition, factors that could  
45 340 give raised CEA levels in the absence of recurrent colorectal cancer, such as chronic lung  
46 341 disease, cirrhosis, chronic pancreatitis, and chronic renal failure were excluded by clinical  
47 342 questioning, chest x-ray, liver function tests, blood urea and electrolytes. Smoking habits and  
48 343 alcohol consumption were also recorded as heavy smoking or drinking, or a change in these  
49 344 habits, can influence CEA levels.  
50 345  
51 346  
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54 349 Figure 3: Trial flow diagram

#### 55 350 *Monitoring of Patients*

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7 352 Clinical follow-up of all patients continued in an identical manner (three monthly for the first  
8 353 two years and six monthly for the next three years) whilst blood for CEA assay was drawn  
9 354 monthly for the first three years and three monthly for the next two years. If the patient  
10 355 remained well and the CEA was within normal limits as defined by a pre-tested algorithm,  
11 356 monitoring continued according to the schedule.  
12 357

#### 12 358 *CEA assay*

13 359 Ten mls of whole blood were taken from each patient. The serum was separated and sent to  
14 360 the Trials Centre in special plastic phials. After logging receipt, the samples were forwarded  
15 361 to the Medical Oncology Department at Charing Cross Hospital for assay. The results were  
16 362 returned to the Trials Centre for recording and action if appropriate. This centralised system  
17 363 ensured that all participating clinicians were kept blind to the CEA results for their patients.  
18 364 It also ensured quality control of the CEA assay as there was no possibility of inter-laboratory  
19 365 variation.  
20 366

21 367 Serum CEA values were measured by double antibody radioimmunoassay. ~~(34-36)(32-34)~~ A  
22 368 bank of serum samples has been retained at -20°C.  
23 369

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#### 24 370 *Monitoring assay compliance pre-randomisation*

25 371 Throughout the trial, compliance with blood sampling was monitored by the secretariat.  
26 372 Clinicians were reminded each month of the patients for whom samples were due; those who  
27 373 had missed the previous visit were highlighted as urgent. The percentage compliance for  
28 374 each participating patient was calculated as the number of samples received divided by those  
29 375 expected x 100. The median time between samples was also calculated. Failure to achieve  
30 376 50% of the expected samples was defined as poor compliance. Since the sensitivity to detect  
31 377 CEA rises in such patients was greatly reduced -they were excluded from randomisation.  
32 378

#### 34 380 *'Significant' Rises in CEA*

35 381 A rise in CEA was defined as 'significant' when the CEA level was greater than 10ng/ml on  
36 382 two successive occasions and one of the following conditions was also met: the CEA level  
37 383 was greater than 20ng/ml on each of two successive occasions *or* the level was rising and the  
38 384 highest value was more than 7ng/ml above the lowest value ever recorded. If a 'significant'  
39 385 rise in CEA occurred, the record of the patient was reviewed at the Trials Centre and  
40 386 provided no evidence of suspected colorectal or other disease was recorded in the CRF, the  
41 387 patient was randomised either into an 'Aggressive' or 'Conventional' arm.  
42 388

42 389 Figure 4: CEA algorithm  
43 390

#### 44 391 *Randomisation*

45 392 Patients were randomised equally between the two arms (1:1). Patients whose compliance  
46 393 was between 50 and 70% or whose immediate post-operative sample had not been received  
47 394 within the 4 to 6 week guideline were randomised in a separate stratum. Randomisation was  
48 395 also stratified by participating clinician. A block size of two was used in order to maintain as  
49 396 close a balance as possible between the two treatment arms.  
50 397

51 398 If the patient was randomised to the 'Aggressive' arm the clinician was informed of the rise  
52 399 immediately by telephone from the trial centre and subsequently in writing and was requested  
53 400 to contact the patient urgently. Patients were informed of their situation including the fact  
54 401 that they had been randomised within the trial to undergo a second-look procedure. This was  
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7 402 then undertaken if the patient gave written informed consent. The surgeon carried out a full  
8 403 clinical work-up to exclude the possibility of a non-malignant cause for the CEA rise (e.g.,  
9 404 change in smoking or drinking habit) and to identify any incurable distant spread. In the  
10 405 absence of these conditions the surgeon undertook a mini-laparotomy, proceeding to full  
11 406 laparotomy with macroscopic clearance of disease, should this be possible.  
12 407 For patients randomised to the 'Conventional' arm no further action was taken; the clinician  
13 408 was neither informed that the CEA had risen nor that the patient had been randomised.  
14 409

15 410 If at any stage a patient in the study developed clinical evidence of recurrent disease the  
16 411 clinician was at liberty to manage the patient according to usual practice. If the disease was  
17 412 in the abdomen and was thought to be treatable by a second-look operation with re-resection,  
18 413 this was ~~perfectly~~ acceptable. **By the nature of the trial design,** the clinician was blind as to  
19 414 whether such patients had been randomised to the 'Conventional' arm of the trial or had not  
20 415 been randomised because the CEA had failed to denote the presence of recurrent disease.  
21 416

#### 21 417 *Second-Look Laparotomy*

22 418 The surgeon was expected to perform a thorough inspection of the abdominal cavity to locate  
23 419 any recurrent disease. Initially a mini-laparotomy was performed; if widespread tumour was  
24 420 detected all that was required prior to closure, was biopsy. Otherwise following a full  
25 421 excision, bimanual palpation of the old scar, inspection and palpation of the pelvic cavity, the  
26 422 small bowel, the mesentery, the retroperitoneum, the colon and rectum and the anastomosis  
27 423 was undertaken. The liver was fully mobilised to determine whether any tumour was present.  
28 424 Detailed dissection of the pelvic and retroperitoneal areas and therapeutic resection were then  
29 425 carried out with the objective of total extirpation of all recurrence. Complete data recording  
30 426 of the procedure along with the results of the histology of all potentially involved sites was  
31 427 required by the trial's office.  
32 428

33 429 For patients in whom a radical resection was achieved after second-look surgery (motivated  
34 430 either on clinical information or because the patient had been randomised to the 'Aggressive'  
35 431 arm) the follow-up schedules for clinical examination and blood sampling reverted to those  
36 432 following the primary operation. However, for patients randomised to the 'Aggressive' arm,  
37 433 clinicians were immediately notified of any further CEA levels above 10ng/ml.  
38 434

#### 38 435 *Death*

39 436 Every patient registered onto the study was 'flagged' with the Office of Population Censuses  
40 437 and Surveys (now ONS) who provide automatic notification of date of death. This enabled  
41 438 the trial centre to receive certified cause of death for all patients.  
42 439  
43 440

#### 44 441 *Trial oversight*

45 442 A Data Monitoring Sub-Committee (DMSC) composed of Working Party members not  
46 443 entering patients into the trial was asked to review the data after the first 100 patients had  
47 444 been randomised, which occurred in January 1988, and again after 200 patients had been  
48 445 randomised in February 1993. At this point it was recommended by the Data Monitoring  
49 446 Committee that the trial stopped since it was very unlikely that any clinically important  
50 447 advantage would be demonstrated for patients undergoing second-look surgery.  
51 448

52 449 Methods of the RIAT process  
53 450

#### 54 451 *The data*

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7 452 The RIAT restorative authors had been warned by the statisticians called in to look at the data  
8 453 in 2003-4 that “the databases were corrupted with key variables no longer  
9 454 abstractable” ~~(37:38)(35:36)~~ We found that the data on paper and on file were accessible and  
10 455 we had no reason to doubt the veracity of individual items. We found that the electronic files  
11 456 had numerous problems with formatting which made the files on the 1447 individual patients  
12 457 difficult to handle but that the data entries were not themselves corrupted.  
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14 459 One of the RIAT restorative authors (KM) had worked in the trials units during the time the  
15 460 CEA Trial data were being accrued and knew the systems in use and their changes but was  
16 461 not directly involved in this trial at any stage.  
17 462

18 463 The questions raised and the problems encountered, were resolved as follows:  
19 464

- 20 465 • The codes indicating that a patient had met the criteria for CEA elevation and  
21 466 whether they were randomised to ‘active’ or ‘Conventional’ arm were preserved and  
22 467 tallied with the number in the 1994 manuscript. ~~(32)(30)~~  
23 468
- 24 469 • There were variations in the way dates were recorded in the database. There had been  
25 470 migrations of data from a ‘Prime’ server using ‘Universe’ to ‘Excel’ and the  
26 471 interpretation of the present authors, with information from contemporary witnesses  
27 472 was that in undertaking the task operators did not always correctly specify these data  
28 473 as ‘dates’ when importing, and/or allowed them to be converted to American date  
29 474 formats. These errors prevented calculations and would have defeated running a  
30 475 survival analysis without correction of the file entries. The dates were however  
31 476 visually readable and not ‘corrupt’. Some could be corrected by running current  
32 477 versions of software. Others were manually corrected by re-entering them in a  
33 478 Microsoft date format. Paper records were available to resolve uncertainties.  
34 479
- 35 480 • The next problem was in linking these three groups of patients (randomised to  
36 481 ‘~~A~~ggressive’, randomised to ‘~~C~~eonventional’ and not randomised) to the dates for  
37 482 survival analysis. Individual patients were uniquely identified in the files by seven  
38 483 digit strings to which letters had been added at the beginning and end, possibly for  
39 484 trial administrators’ checklists or subgroup identification. Once we had established  
40 485 that the initial and terminal letters were redundant for analysis of the primary  
41 486 endpoint, we were able to write code to restore the seven digit strings.  
42 487
- 43 488 • It was evident that the seven digits did not represent a simple sequence but certain  
44 489 positions identified particular characteristics, such as participating centre. We  
45 490 recognised a consistent pattern of mismatch in the fourth digit, -a zero in one file was  
46 491 an 8 in the other with all other digits remaining the same. It was suggested to us that  
47 492 the fourth digit replacement was used to identify patients suitable for *post hoc*  
48 493 subgroup analyses but no documentation was found to confirm this. By checking  
49 494 back to the dates of birth we were able to confirm that this systematic correction  
50 495 resolved the problem and most of the data were then usable.  
51 496
- 52 497 • By ranking all the data in the paired files for line by line visual inspection residual  
53 498 discrepancies were identified. Scrutinising the digit strings allowed for seven of the  
54 499 remaining eight pairs to be reconciled and verified on dates of birth. We failed to  
55 500 resolve only one out of 1447 records in each file. This patient had not been  
56 501 randomised.

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- 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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551 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 <sup>1</sup>	36 (33.3)	38 (35.2)
Dukes' C <sup>2</sup>	17 (15.7)	10 ( 9.3)
Missing	4 ( 3.7)	6 ( 5.6)

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

556  
557 Of the patients randomised to the 'Aggressive' arm 83 (77%) had recurrent cancer identified  
558 and 62 (57%) patients had 'second-look' surgery. In patients randomised to the  
559 'Conventional' arm 89 (82%) had developed recurrent disease by the date of analysis. In  
560 these 26 (24%) second-look procedures were undertaken. By February 1993, 91/108 in the  
561 the 'Aggressive arm' had died and 88/108 patients had died in the 'Conventional' arm  
562 (relative risk = 1.16, 95% CI 0.87-1.37), ~~(32)(30)~~. It was considered by the data monitoring  
563 committee to be "highly unlikely that any survival advantage would be demonstrated for  
564 patients undergoing second-look surgery". This was communicated to the chief investigator.

#### 565 *RIAT restoration and updated survival analysis*

566  
567 The data were restored by the RIAT authors for 1446 of 1447 patients to the extent that the  
568 RIAT authors were confident of their dates of birth, death and whether they met criteria for  
569 entry into the controlled trial and then to which arm they were allocated.

570  
571 The electronic records were intact with respect to the identity of the patients, which patients  
572 had reached the criteria for randomisation, and the trial arm to which they had been randomly  
573 allocated for all 216 patients who were randomised. The sex, age, primary site and Dukes'  
574 stage as recorded in the 1994 manuscript are shown in Table 1.

575  
576 Certification of death was obtained from ONS on behalf of the RIAT restorative authors for  
577 204 of 216 randomised patients who died between 17/10/1983 and 08/09/2011. There were  
578 equal numbers of patients in the two arms (108) and equal numbers of death dates were  
579 retrieved (102). We also have dates of death in 862 of the 1230 patients who were not  
580 randomised. Kaplan Meier analysis in these three groups is shown in Figure 6, showing  
581 survival of the 1230 participants who entered the trial but were not randomised and the 108  
582 participants randomised into each arm.

#### 583 584 Figure 6 Kaplan Meier analysis

585  
586 The lead time conferred by CEA monitoring, defined as the median time to clinically  
587 detected disease for patients randomised to the 'Conventional' arm, was 323 days (95%  
588 confidence interval (CI) 203-443). This analysis included censored observations on 23  
589 patients, however only five of these had a censored time less than the lead time. It was

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590 regarded as unlikely, therefore, that the lead time would decrease as further events occur. The  
 591 analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12  
 592 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs  
 593 44% and 97% vs 70% at a year. The RIAT authors did not repeat this analysis.

#### 594 595 596 Discussion

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

599 “Does a policy of CEA-prompted second-look surgery following ‘curative’ resection  
 600 of colorectal cancer produce a decrease in morbidity and mortality due to tumour  
 601 recurrence, despite sequelae of second look surgery?”

602  
 603 The answer is that acting on CEA elevation by second-look surgery did not reduce mortality  
 604 compared with patients in whom similar CEA elevation remained unknown. This negative  
 605 finding led to the closing of the trial in 1994(2:24)(21:22) and we confirm it here. There was  
 606 small non-significant excess of deaths in the ‘Aggressive’ arm. The burden of morbidity  
 607 attributable to the greater number of investigations and operations was not captured by the  
 608 trial protocol nor indeed the ‘needless anxiety’ which concerned Moertel(23)(20) and the  
 609 authors of the CEA trial protocol.(1)(4)

610  
 611 The second planned analysis was to obtain an accurate picture of the ‘lead time’ produced by  
 612 CEA compared to clinical pick up of patients with recurrence. CEA monitoring did pick up  
 613 patients considerably sooner than the clinical methods available at the time by ~~s~~+11 months  
 614 (95% CI 7-14 months).

615  
 616 CEA monitoring ~~is currently recommended~~ for the ~~is~~ purpose of early detection of  
 617 asymptomatic cancer is currently recommended at least every 6 months in the first three  
 618 years. In addition a minimum of two CT scans are recommended in the first three  
 619 years.(39)(37) The FACS trial, recently reported, has also shown ~~ed~~ no survival advantage  
 620 compared from CEA monitoring compared with minimum follow-up.(40)(38) More  
 621 operations were performed with ‘curative intent’-for recurrent cancer in those having more  
 622 intensive monitoring and there were more deaths (18.2%[164/901] vs 15.9% [48/301];  
 623 difference, 2.3%; 95%CI, -2.6%to 7.1%). These results are similar to the findings in the  
 624 CEA trial. Although the phrase ‘curative intent’ occurs about 40 times in the manuscript,  
 625 longer survival is not evident.

626  
 627 The third and fourth intentions set out by the CEA trialists were c) to obtain further data  
 628 relating CEA levels to tumour histology and topography and d) a large data base on the  
 629 natural history of colorectal cancer. Multiple CEA assay results exist in the data we hold for  
 630 1446 patients and it would be possible to link these to survival as a result of the RIAT  
 631 restorative work.

632  
 633 With respect to the natural history of colorectal cancer although we trust the death  
 634 certification data for the date of death it has been shown that “at least a third of all death  
 635 certificates are likely to be incorrect”(41)(39). No doubt aware of this and seeking much  
 636 more detailed information, the CEA Trialists had asked for detailed post-mortem  
 637 examinations. It appears that it was disagreement concerning explanatory analyses which  
 638 contributed to the failure to publish the primary outcome of interest.(32)(30) The purpose of  
 639 such analyses would be is-to discover subsets of patients in whom there was a benefit from

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7 640 the intervention under evaluation and to thus determine the characteristics of patients in  
8 641 whom the intervention might have had a beneficial effect by analysis of mediators and  
9 642 moderators. ~~(42)(40)~~ There is a general objection to this exercise because it can lead to  
10 643 spurious associations. ~~(43;44)(41;42)~~ Furthermore when there is no overall benefit found, as  
11 644 in the CEA Second-Look Trial, any subgroup(s) where there is a positive association between  
12 645 intervention and outcome must be balanced by one or more other groups where there was net  
13 646 harm. The methods section of the 1994 manuscript states 'Subgroup analyses have been  
14 647 performed to address specific issues but these need to be interpreted with appropriate  
15 648 caution.'~~(32)~~ In the event no ~~There were~~ no completed subset analyses ~~were~~ in the 1994  
16 649 paper and the closing notes between the authors are on the matter of a subset analysis. ~~W~~  
17 650 we have not attempted any in restoring the trial.

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18 651  
19 652 The answer to the primary research question was clear in 1993 and was the explicit reason for  
20 653 stopping the trial: it was improbable that a benefit from CEA prompted second-look surgery  
21 654 had been missed and in the absence of benefit there was net harm being done to the patients.  
22 655 The forms of second look surgery now widely practiced in colorectal cancer are liver and  
23 656 lung resection of metastases.

- 24 657
- 25 658 • Full mobilisation of the liver at second-look laparotomy was included in the CEA  
26 659 Trial protocol. Hepatic resection has entered routine practice based on observational  
27 660 data ~~(45)(43)~~ and an opportunity to do a randomised trial, for which a power  
28 661 calculation was proposed in 1992 from the Mayo Clinic ~~(46)(44)~~ was not  
29 662 taken. ~~(25)(23)~~
  - 30 663 • Two patients had a thoracotomy prompted by CEA elevation. Pulmonary  
31 664 metastasectomy for colorectal cancer is, after primary lung cancer, the second  
32 665 commonest thoracic cancer operation and is the subject of an ongoing randomised  
33 666 controlled trial. ~~(47)(45)~~

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34 667  
35 668 The CEA Trial findings have been corroborated by the larger FACS trial. If the CEA trial  
36 669 results had been made available in 1994, and there is no evident reason why they should not  
37 670 have been, a more critical scrutiny of the evidence base that was used to bring liver and lung  
38 671 metastasectomy into practice. ~~(25;30)(23;28)~~ might have been undertaken. The CEA Trial  
39 672 was a well-conceived and meticulously executed randomised trial and we hope that  
40 673 publishing it now more than twenty years after its completion will indicate the possibility of  
41 674 more randomised trials in surgery. ~~(48)(46)~~

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7 675 Legends

8 676  
9 677 Figure 1. The “Working Party” that produced the protocol in 1982 for the CEA Second-Look  
10 678 Surgery trial. ~~(1)(4)~~

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11 680 Figure 2. Illustration of operative findings in six successive operations seeking recurrence of  
12 681 colorectal cancer. ~~(15)(12)~~

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13 682  
14 683 Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol. ~~(1)(4)~~

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15 684  
16 685 Figure 4. Decision making algorithm for CEA to trigger second-look surgery. ~~(15)(12)~~

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17 686  
18 687 Figure 5. Flow chart of enrolled and ultimately randomised patients. ‘Blind’ in the bottom left  
19 688 box means that the clinical teams were unaware of the elevated CEA discovered and were  
20 689 unaware that the patients have been randomised. They were indistinguishable amongst the  
21 690 1230 non-randomised patients who were being followed-up. (See Figure 6)

22 691  
23 692 Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446)  
24 693 following potentially curative colorectal cancer surgery. Patients who had CEA elevation  
25 694 according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA  
26 695 revealed to their surgeons (red) or concealed (blue). Date of death was confirmed from  
27 696 Office for National Statistics in 104/108 in each arm. The green line is for all other patients.  
28 697 (N=862 of 1230) Some would have had clinically evident early recurrence precluding  
29 698 randomisation. The initial plateau is an illustration of a death free interval ~~(49)(47)~~ or  
30 699 “immortal time bias” ~~(50)(48)~~. Patients in prospective studies may have a built in obligatory  
31 700 survival time from some starting point in order to attain the requirements to be included in the  
32 701 data set. This is an artefact but may be absorbed into survival time adding to and not readily  
33 702 distinguished from survival time attributed to treatment.

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



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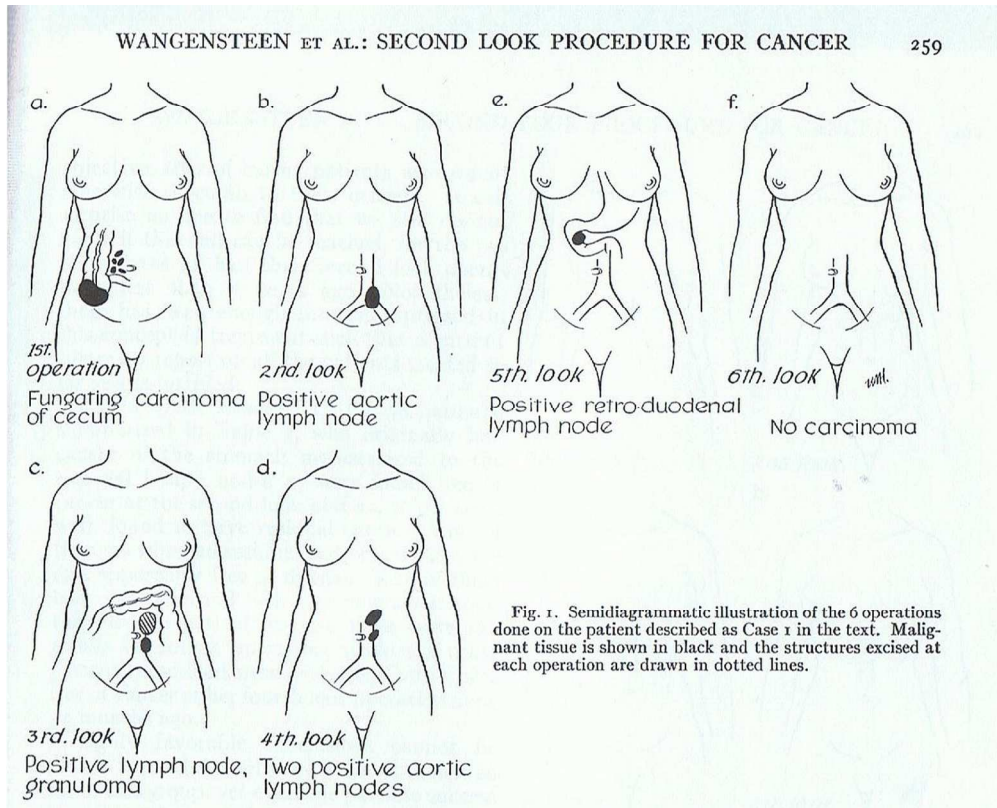


Figure 2. Illustration of operative findings in six successive operations seeking recurrence of colorectal cancer.[22]  
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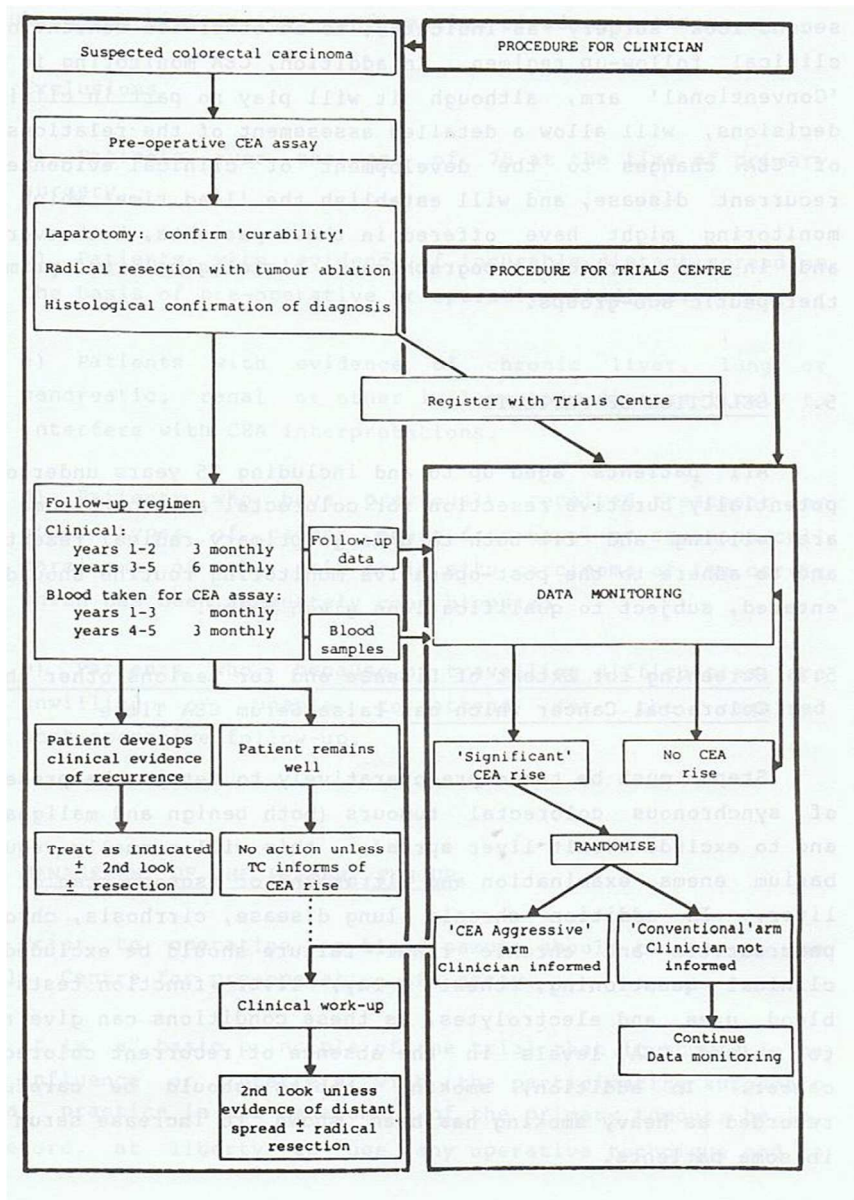


Figure 3. Flow diagram of the Second-Look Surgery trial from the 1982 protocol.[4]  
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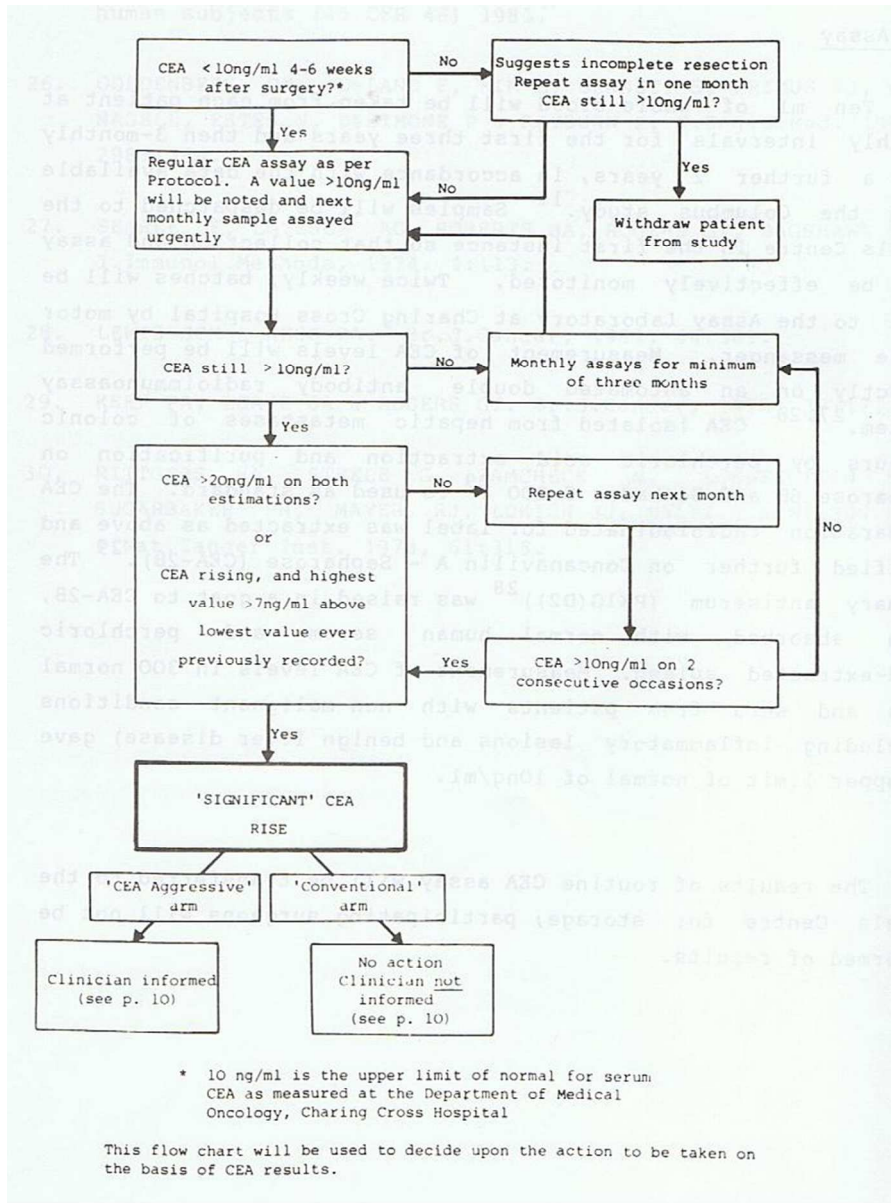


Figure 4. Decision making algorithm for CEA to trigger second-look surgery.[22] 66x90mm (300 x 300 DPI)

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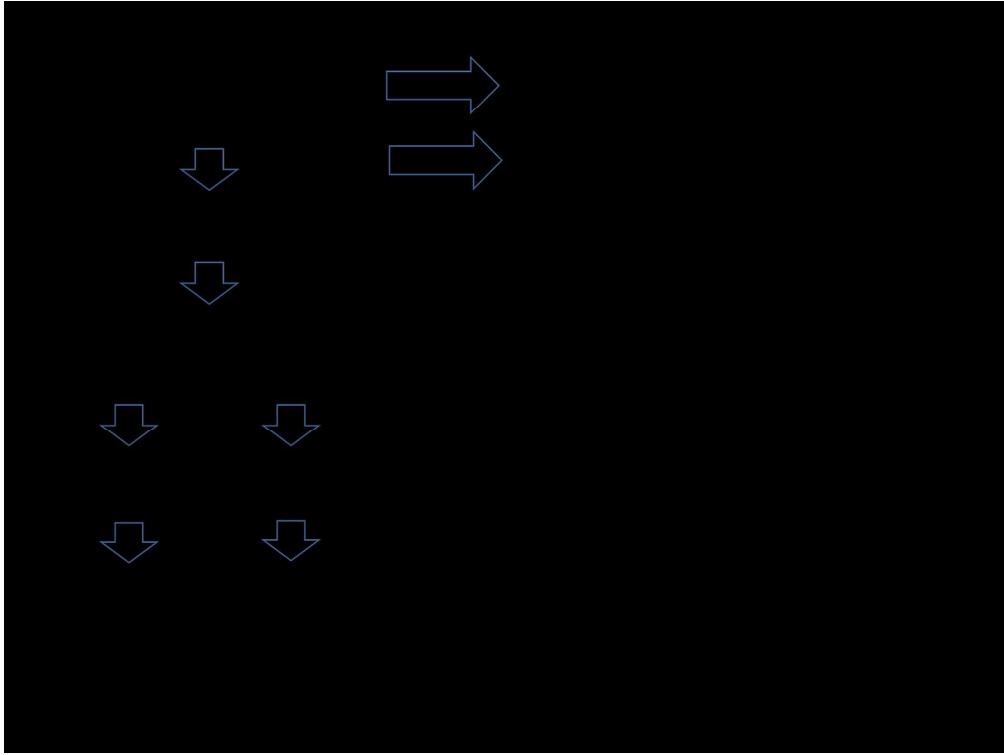


Figure 5. Flow chart of enrolled and ultimately randomised patients  
119x90mm (300 x 300 DPI)

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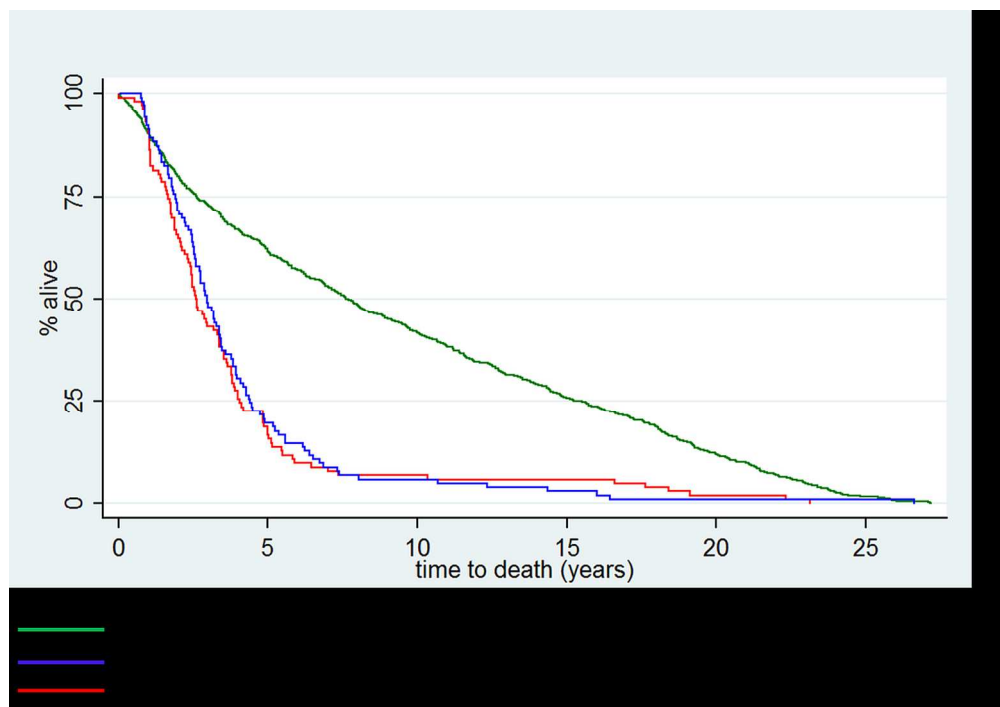


Figure 6. Survival from date of recruitment into the CEA Second-Look Trial (N=1446) following potentially curative colorectal cancer surgery. Patients who had CEA elevation according to the trial criteria (N=216) were randomly allocated in equal groups to have CEA revealed to their surgeons (red) or 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.

## 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
<b>Title and abstract</b>						
	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	
<b>Introduction</b>						
Background and objectives	2a	Scientific background and explanation of rationale	5-6	4-9	None written	
	2b	Specific objectives or hypotheses	3	2	2	
<b>Methods</b>						
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	This was of course implicit that these were in units performing colorectal cancer
					CEA assays	
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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			
<b>Results</b>						
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.
<b>Discussion</b>						
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			
<b>Other information</b>						
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	

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\* 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](http://www.consort-statement.org) for more details.

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