Listen to the podcast by the authors at bmj.com/multimedia/podcasts http://www.bmj.com/multimedia/podcasts

Operating to remove recurrent colorectal cancer: have we got it right?

A randomised controlled trial that remained unpublished for 20 years casts doubt on the survival benefit of further surgery after curative resection of colorectal cancer. **Tom Treasure and colleagues** tell the story of the first trial to be analysed under the restoring invisible and abandoned trials initiative and discuss what it means today

Fig 1| Rediscovered data files for the CEA second look study

Old, unpublished clinical trials ordinarily remain unpublished, their results unable to add to the scientific knowledge base, their implications unable to affect practice. But the new restoring invisible and abandoned trials (RIAT) initiative offers a way forward. The RIAT concept allows third parties to publish previously unpublished trials when the original trialists or sponsors fail to do so.[1] Last June, the editors of *BMJ* and *PLoS Medicine* called on "researchers and editors to help restore invisible and abandoned trials" by taking unpublished study results and submitting them for publication.[2] We were among the first to register our intent to RIAT[3] and have now published a two decade old trial that examined the use of carcinoembryonic antigen (CEA) to prompt "second look" surgery in colorectal cancer.[4]

Role of CEA and second look surgery

In modern management, a newly diagnosed colorectal cancer is staged, graded, and discussed by a team of surgeons, oncologists, and radiologists with a view to curative surgery if possible. About 16% of patients operated on will have recurrence of cancer within five years.[5] Monitoring with the tumour marker CEA is recommended to identify these people as early as possible. The UK's National Institute of Health and Care Excellence recommends CEA tests at least every six months in the first three years, plus a minimum of two computed tomograms of the chest, abdomen, and pelvis.[6] If CEA level is raised and metastases are detected in the liver or lungs, patients are assessed for surgery to remove the metastases with intent to cure.

Before tumour markers were available, there was a drive to monitor for recurrence by "second look" surgery. Second look surgery originated in the 1950s and was promoted in the 1970s. Asymptomatic patients at high risk of recurrence, such as those who had had affected lymph nodes, were reoperated on at six monthly intervals, with recurrences resected when found. If cancer was found patients were scheduled for further operations (up to a total of six) until the abdomen remained free of cancer.[7]

This approach to management was not without its critics. Colorectal surgeon William Slack wrote in 1982 that this blanket policy might produce some cures but entailed high rates of negative laparotomy and an unacceptable operative mortality rate.[8] Nevertheless, an analysis of 15 years' experience of following up patients at his hospital[9] concluded that active cancer had to be detected earlier than was possible clinically if repeat surgery was to benefit patients. This formed the basis for the CEA second look trial for colorectal cancer, which Slack headed.

Before tumour markers were available, there was a drive to monitor for recurrence by "second look" surgery

By the late 1970s it had been established that raised CEA levels detected cancer recurrence on average four months before it was clinically evident[10] and had a low false positive rate.[11 12] Testing could spare patients without raised CEA levels needless second look surgery, and early detection was expected to lead to a better prospect of resecting all recurrent disease than when clinical criteria were used to prompt reoperation. It was not clear, however, whether this would result in better survival, which prompted a National Institutes of Health consensus statement calling for trials into CEA with second look surgery in 1981.[13] Slack and colleagues incorporated CEA testing into a study of second look surgery. The design, by identifying patients with active cancer at the earliest possible point, gave surgery the best chance of being effective.

What the trial did

The Carcinoembryonic Antigen Second Look Trial set out to enrol 2000 participants who had had curative resection of colorectal cancer, 500 of whom were expected to have a rise in CEA level indicative of recurrence on regular monitoring. Half of those with a CEA rise were randomised to immediate second look surgery and half to continued routine clinical care, which at the time was clinical review every three months for the first year, then six monthly until there was clinical suspicion of recurrence. At this point second look surgery was also to be considered. The hypothesis was that CEA monitoring would increase the success rate of second look procedures, in terms of macroscopic clearance, from 25% to 55%. The trial was powered to detect a resulting improvement in survival from 10% to 22% at five years.[8 4] According to the protocol, surgeons were to resect any recurrence at the surgical site, in the peritoneum, or in lymph nodes. They were also to mobilise the liver to identify and resect metastases.

The trial started in 1982 and by 1993 had recruited 1447 of the intended 2000 participants and randomised 216 when it was stopped early. The data monitoring committee thought it was highly unlikely that any survival advantage would ever be shown.[14 15] When the trial was unblinded it was found that there were more deaths in the active arm than the control arm (91 *v* 88; relative risk=1.16, 95% confidence interval 0.87 to 1.37).[4] This important finding might have

How the CEA Second Look Trial was left behind by events

1954
Wangensteen (below) advocated second look surgery in asymptomatic patients after colorectal cancer[7]

1971-78
Resection of recurrent cancer after potentially curative resection of colorectal cancer was believed to sometimes lead to "cure"[23-25]

1974-80
CEA was shown to detect asymptomatic recurrence of colorectal cancer[10 26-29]

1981
National Institutes of Health consensus called for a trial of CEA[30]

1982
Slack and Northover started the CEA Second Look trial[8]

1982-89
Hughes published an international registry of hepatic metastases resection from 24 institutions in North America, England, and Germany. After excluding 30 day mortality, they reported five year survival of 30%[31-34]

1990-91
Surgeons at Erlangen University Hospital, Germany (above), publish their results for liver resections. After exclusion of 5.5% postoperative death five year survival was 39%[35-37]

1992

Memorial Sloan-Kettering Cancer Center in New York (left) published 10 year results of pulmonary metastasectomy in colorectal cancer. Five and 10 year survival rates were 40% and 30%, respectively[38]

Mayo Clinic surgeons publish the power calculation for a randomised trial of liver resection suggesting that 36 patients would have been sufficient to prove benefit[39]

1994
CEA Second Look Trial results available[14 15]

Erlangen group wrote in the *Lancet*, "The benefit in outcome provided by resection of colorectal liver metastases had been clearly demonstrated' based on 30% five-year disease-free survival amongst the 10-20% of their patients selected for this surgery"[40]

Erlangen group wrote "trials on ... effectiveness of hepatic resection for metastatic colorectal cancer [would be] not only obsolete but unethical"[41]

influenced practice, but it remained unpublished for 20 years.

How the trial was lost

The study ran for longer than expected and was affected by various organisational changes. Recruitment was slow, and only 15% of patients met the stringent criteria for randomisation rather than the 25% predicted. During the course of recruitment, the trial unit moved from King's College Hospital, London, to University College London. Slack, the chief investigator, retired and John Northover, who had been a driving force throughout, took on that role.

Although the study was stopped early, there was a clear intention to publish. The primary outcome, survival, was recorded in an abandoned version of the manuscript dated 6 July 1994 that we found in the archive and had been revealed publicly in a letter to *JAMA*[14] and in a conference abstract in the *British Journal of Cancer*.[15]

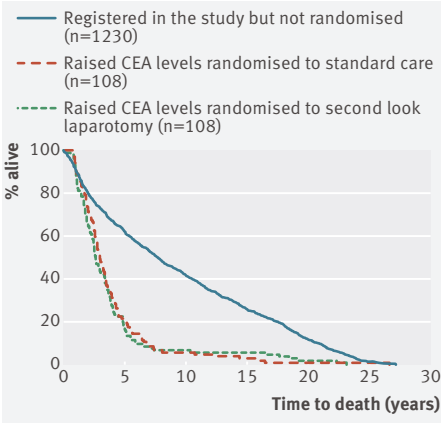

Fig 2 | Kaplan-Meier analysis of survival among participants in the Carcinoembryonic Antigen (CEA) Second Look Trial[4]

The methods and results appear complete in the manuscript prepared for submission in 1994,but the discussion halts after three lines with a comment about the identification and analysis of subsets. Our interpretation is that differences over attempts to perform post hoc exploratory analyses may have led to the breakdown of the efforts to publish in 1994.

The data then languished until after the sudden death of the trial statistician, Kenneth MacRae, in April 2002. The study was referred to two trial statisticians outside the trial centre, who looked at the electronic files around 2003. They failed to access the data to their satisfaction, deeming them "corrupted," and a decision was made to not reopen the analysis.

Piecing the trial back together

In the face of increasing referrals for pulmonary metastasectomy in colorectal trials, a proposal was made for a trial in 2009[16] comparing active monitoring with active monitoring plus pulmonary metastasectomy in patients who had curative resection for colorectal cancer, the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial.[17] The trial was designed to resolve the paradox that patients who had pulmonary metastases detected by CEA were being referred for metastasectomy despite consistent reports that raised CEA levels were associated with poor survival after pulmonary metastasectomy.[18 19] As the data from the second look study were relevant to PulMiCC, in August 2009 we asked Northover what had happened to the results. He believed the data to be irretrievably lost. Michael Baum, who headed the trial's data monitoring committee, thought the same. In October 2009 we contacted others involved at the time. The UCL clinical trials centre response was that the data were corrupted.

One of us, KM, had recently left UCL and was aware of the trial's history and electronic database problems but she knew that the files were still in the unit (fig 1). On 6 November 2009 TT asked the current director of the trial centre, Jonathan Ledermann, for access to the data. We were eventually given access in March 2011. Staff at the trial centre retrieved the archived electronic files and the centre's director authorised our access to an anonymised copy, saying, "The problem is that the data are in a total mess."

We discovered that the data were not corrupted but difficult to analyse. The 1980s had been a time of rapid development in computing and software, demanding steep learning curves in its implementation. File transfers by temporary staff and various informal codes inserted into the data had made data extraction seem impossible at first sight, but we were able to restore trustworthy and usable records for 1446 of the 1447 participants. We then updated the survival data to September 2011. The data available in February 1993 were that 91/108 patients had died in the "aggressive" arm and 88/108 in the "conventional" arm (relative risk=1.16, 95% confidence interval 0.87 to 1.37). Our updated analysis confirms that there is no hint of a survival advantage associated with knowledge of the CEA (fig 2).[4]

We spoke to as many as we could find of those listed in the trial documents at the outset[8] and in the draft manuscript to check we had made sense of the data and had not overlooked anything. It was clear that the trial team had broken up in disarray, but those we spoke to regretted that the trial had not been published and supported us now doing so.

What the trial means today

By the time that the CEA trial closed clinical practice had shifted. CEA testing had become commonplace after curative resection of colorectal cancer, and liver and lung metastasectomy had been adopted based on observational evidence (box).[20 21] In 1992 the Mayo Clinic proposed that a randomised trial should be done to determine the survival difference resulting from resection of liver metastases compared with no resection.[22] It proposed that if the difference in five year survival with liver metastasectomy was 25% versus 1%, as was being claimed, only 36 randomised patients would be needed to confirm an effect. However, the trial did not take place because of a general view that "it would be difficult to obtain informed consent from patients randomised to no treatment despite resectable disease and, in view of reported results of surgical resection, it is unlikely that ethical committees would agree to such a trial."[35]

Although the CEA second look trial found no benefit from an overall policy of detecting and resecting disseminated cancer, organ specific resection of metastases has become common practice. The recent Follow-up After Colorectal Surgery (FACS) trial[5] tested the effectiveness of intensive monitoring with CEA testing, computed tomography, or both compared with no scheduled follow-up except a single computed tomogram of the chest, abdomen, and pelvis at 12 to 18 months if requested at study entry by the hospital clinician.[5] There was a higher death rate in the intensive monitoring group (18.2% (164/901) *v* 15.9% (48/301); difference 2.3%, 95% CI −2.6% to 7.1%). The study had originally intended to estimate the difference in overall survival but "in 2007 when it became clear that we could not recruit the number of participants necessary to estimate an effect on overall survival with adequate statistical power" the primary outcome was changed to "surgical treatment with curative intent." This was not, in fact, "curative" surgery since it is not associated with higher survival rates. The FACS trial results are in accordance with the absence of survival benefit found in the CEA second look trial in 1994.

Methods of detection, imaging, and surgical resection have changed over the intervening 20 years and those committed to resecting metastases may well regard the results of the restored CEA Second Look trial as irrelevant. We take a different view. We do not believe that the findings of the CEA trial can be readily discounted but rather consider that the onus is on those promoting unproved operations to test their effectiveness in controlled trials.

Contrary to a commonly held view among surgeons, patients are not the obstacle to trials. In the National Cancer Patient Experience Survey of over 70 000 patients in the British National Health Service, around two thirds did not have cancer research discussed with them, though half would have preferred that it had been.[42] Of the patients who were made aware of research, two thirds went on to be included in research studies. Patients are entitled to a voice, but are we listening?

We believe that the new evidence should fuel uncertainty about present day second look surgery for colorectal cancer in its various forms and hope that it will give some encouragement to undertake the randomised trials that are needed. Within the NHS these studies could be promoted by the National Institute for Health Research and the National Cancer Research Institute.

Tom Treasure professor, University College London Clinical Operational Research Unit, London, UK

Kathryn Monson researcher, Sussex Health Outcomes Research and Education in Cancer (SHORE-C), Brighton and Sussex Medical School, University of Sussex, Falmer, UK

Francesca Fiorentino research fellow, Imperial College, Cardiothoracic Surgery Department, London, UK

Christopher Russell surgeon, London, UK

Correspondence to: T Treasure **tom.treasure@gmail.com**

We thank Jonathan Ledermann, director of the centre where the CEA files were stored, and Sharon Forsyth for her help in accessing the CEA trial data and updating the Office for National Statistics records for death registration. We authors also met the following people who were members of the 1982 working party for the study or listed as contributors in the 1994 draft manuscript: M Baum, R H J Begent, H Ellis, J Houghton, M Irving, C A Lennon, J M A Northover, W W Slack, and C B Wood. We thank them for frank discussions concerning the progress of the study and the factors leading to its closure and the abandonment of publication.

Contributors and sources: TT is chief investigator and CR is chair of the trial steering committee of the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial. They both worked at the Middlesex Hospital and knew about the CEA Second Look Trial from its inception in 1982. KM works on the PulMiCC trial and was previously in the UCL Trials Unit during enrolment to the CEA Second-Look Trial, but she had not worked on it. KM and TT restored the data under the leadership of CR. FF worked with TT on a research programme of systematic reviews and analytical studies related to surgery. She did the analysis. The authors interviewed as many of those involved with the second look trial as could be found.

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2014;348:g2085

ANSWERS TO ENDGAMES, p 38

For long answers go to the Education channel on bmj.com

ANATOMY QUIZ

Axial computed tomography of the skull base

A: Facial canal (right) and facial nerve (CN VII)

B: Foramen spinosum (right), meningeal branch of mandibular division of trigeminal nerve (CN V), and lesser petrosal nerve (branch of CN IX)

C: Foramen ovale (right) and mandibular division of the trigeminal nerve (CN V)

D: Carotid canal (left) and internal carotid plexus

E: Jugular foramen (left), glossopharyngeal nerve (CN IX), vagus nerve (CN X), and accessory nerve (CN XI)

STATISTICAL QUESTION

What is a crossover trial?

Statements *b* and *c* are true, whereas *a* and *d* are false.

PICTURE QUIZ A 68 year old woman with deteriorating hearing

1 Given the patient's age, the insidious onset, the normal ENT examination results, and the typical "ski slope" loss on the audiogram, the diagnosis is probably age related hearing loss, otherwise known as presbycusis.

2 The pure tone audiogram shows bilateral symmetrical sensorineural hearing loss, increasing in severity as the frequency increases.

3 The presence of asymmetrical sensorineural hearing loss on audiometry should raise the suspicion of a rare underlying cause, such as an acoustic neuroma, and further investigation (imaging) may be needed. If symptoms are sudden in onset, they should be treated as an emergency that requires urgent steroid treatment and should be discussed with the ENT department on the day of presentation. If the examination is abnormal or the presentation unusual, the patient should also be referred for a specialist opinion.

4 Patients with presbycusis should be referred to audiology for hearing aids and audiological rehabilitation; they should also be referred for hearing therapy. This allows patients to gain maximal benefit in terms of amplification of sound, advice, and techniques on dealing with and managing their hearing loss, as well as discussion of any adjuvant techniques that might help.