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EDITOR'S CHOICE

Colorectal cancer: a cautionary tale

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This week our sister journal *BMJ Open* publishes a report of a trial that was stopped early in 1993 and was never published.[1] The report, by Tom Treasure and colleagues, is one of the first outputs of the "restoring invisible and abandoned trials" (RIAT) initiative, launched in an article in *The BMJ* last year.[2] And in this week's journal Treasure and colleagues tell us the story of the trial, what its abandonment meant for the way clinical practice developed in the intervening years, and what its restored findings mean today.[3]

The trial sought to discover whether patients who had had a colonic cancer resected could be spared routine "second look" surgery and might survive longer if they had regular monitoring of the tumour marker carcinoembryonic antigen (CEA). Second look surgery, by which patients underwent laparotomy and, if necessary, further resection every six months or so, was the standard of care, but it carried the risk of operative morbidity and mortality. It was thought that patients with raised CEA levels might be spared this unnecessary surgery.

The trial started in 1982. By 1993 it had randomised 216 patients with raised CEA levels to either immediate second look surgery or regular clinical review and intervention, if needed. At that stage the data monitoring committee decided it was highly unlikely that any survival benefit would be shown and stopped the trial. As Treasure and colleagues explain, when the trial was unblinded it was found that there were slightly more deaths in the active arm than in the control arm.

This important finding remained unpublished for 20 years. Instead, the treatment of patients with colorectal cancer was guided by observational studies, registry data, and case series. CEA testing after curative resection became the norm, and detection and resection of liver and lung metastases is now commonplace. The practice has not gone undisputed over the years. Claims that metastasectomy increased five year survival by up to 25% led surgeons at the Mayo Clinic in the United States to publish a power calculation showing that they would need to randomise only 36 patients to confirm an effect. But further trials were hampered by the view that it would be hard to get ethical approval or informed consent to randomise patients to no treatment if they had resectable metastases.

The story of how Treasure and his colleagues discovered the abandoned data is worth reading. It took them five years to extract, analyse, and write up the results. Future patients may well be in their debt. Their updated analysis confirms that there is "no hint of a survival advantage associated with knowledge of the CEA." The Follow-up After Colorectal Surgery (FACS) trial, recently published in *JAMA*,[4] confirmed the lack of survival benefit, finding a higher death rate in patients who were intensively monitored.

This cautionary tale shows yet again that we can't rely on observational data to decide whether a treatment is effective, that we should nurture rather than dismiss clinical uncertainty and scientific equipoise, that randomisation should be our default setting, and that all trials should be registered and all results reported, as the AllTrials campaign urges (alltrials.net).

1 Treasure T, Monson K, Fiorentino F, Russell RCG. The CEA Second Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. *BMJ Open* 2014;4:e004385.
2 Doshi P, Dickersin K, Healy D, Vedula SS, Jefferson T. Restoring invisible and abandoned trials: a call for people to publish the findings. *BMJ* 2013;346:f2865.
3 Treasure T, Monson K, Fiorentino F, Russell C. Operating to remove recurrent colorectal cancer: have we got it right? *BMJ* 2014;348:g2085.
4 5 Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014;311:263-70.

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