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If a picture is worth a thousand words, take a good look at the picture: survival after liver metastasectomy for colorectal cancer.

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Introduction
An analysis of NHS data published in by Morris et al in 2010 is widely used as evidence in support of liver metastasectomy for colorectal cancer and its wider application. Recent evidence concerning better overall survival for patients with metastatic colorectal cancer challenges the notional assumptions about what survival would be without metastasectomy. Earlier detection of metastases for local treatments has not resulted in a survival benefit.

Materials and Methods
The interpretation of its central graphical display is critically reviewed and the common limitations of the analysis of registry data and resulting immortal time bias are explored.

Results and Discussion
Recent evidence, including the 2017 CLOCC trial report make the original interpretation of the analysis suspect. Randomised trials are essential to detect a treatment effect of specific interventions among variable disease progressions, selection bias, and multiple and repeated treatments that are inherent in the management of advanced cancer.

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Introduction

Operations to resect colorectal cancer metastases have been increasing.[1] The increasing use of a range of image guided ablative treatments for blood borne metastases will probably now lead to more and repeated interventions in the hope of improving survival with a lower risk of morbidity.[2;3] But there are no controlled trials to support this belief and there are reasons for doubt that there is any overall survival benefit from such interventions:

1. Authors of a recent systematic review and meta-analysis praised oncologists for performing randomised controlled trials (RCTs) of systemic therapies while noting that there is no RCT evidence to support the use of surgical metastasectomy. The survival in patients treated systemically has improved, undermining the presumption, based on observational data, of an overall survival benefit from local interventions.[1]

2. Policies of more intensive monitoring after primary resection have consistently brought forward the identification of metastases suitable for metastasectomy, generally by about 1-2 years. But a meta-analysis of 11 randomised trials of these policies showed no demonstrable survival benefit from earlier detection.[4]

The apparent association between more treatments and better survival may be an example of reverse causation: increasing numbers of metastasectomy operations may be a consequence of the availability of more surviving patients, rather than metastasectomy operations contributing to survival.[1]

An analysis performed by one of us (EM) was part of a multidisciplinary collaboration using NHS data.[5] It has been cited by 195 related articles.* In peer reviewed studies (for example [6-8]) the analysis is cited appropriately. Our concern is that at meetings designed to disseminate knowledge, a slide of the central picture of the results (Figure) is offered as evidence of clinical effectiveness without adequate explanation. (Table 1) The purpose of this Short Report is to provide a better explanation of that graph.

Materials and Methods

In the study published in the British Journal of Surgery (BJS), linked cancer registry and Hospital Episode Statistics (HES) data were obtained from the National Cancer Data Repository (NCDR) to provide information on all individuals who had surgical excision of a primary colorectal cancer in the English NHS between 1 January 1998 and 30 June 2004.[5] These patients were tracked through HES data to determine whether they subsequently had a liver resection within three years of resection of their primary tumour. Details of the data and the analysis are provided in the paper.[5]

Results and Discussion

When two or more lines are put on a survival graph it is tempting to make a direct visual comparison. In a fair test of treatments[9] these would be data derived from a randomised controlled trial so that any difference can be reasonably attributed to the difference in treatment and must be tested for how unlikely the difference might have been to chance. This does not apply to any of the lines on this graph.

* https://www.ncbi.nlm.nih.gov/pubmed/20632280

Three of the lines in the figures represent data on patients from NCDR: all patients, those with Stage III (locally spread), and Stage IV (distantly metastasised) as indicated in the key. They are population-based data, including everyone in the country. They are categorised by cancer stage at a common starting point: the date of primary colorectal cancer resection. There would have been other characteristics which influenced selection for primary resection. Some patients would have had other treatments before and/or after primary resection, and so apparent stage-dependent survival is inescapably confounded by positive and negative treatment effects. These confounding factors should be borne in mind when inferences are drawn from visual comparisons. Nevertheless the lines have the characteristic shape of cancer registry data: early decline followed by a levelling off. This is because the distribution of survival times includes a spectrum of patients, ranging from those who are entered into the data set shortly before their death at the left hand end, to long term survivors at the right hand end.

The fourth line on the graph (dashed light blue) shows the survival of patients who also underwent liver metastasectomy, starting from the date of that operation. Its shape is very different, with a plateau and subsequent fall. We know from the HES data that only 2.7% of patients with colorectal cancer had metastasectomy. Selection of such patients is on the basis of repeatedly demonstrated prognostic factors.[6;10;11] The time interval since first considering metastasectomy provides more information about the pace of disease and possible prognosis. Other relevant prognostic factors may come to light such as occult nodal disease and metastasis to other sites leading to patients being selected out. Further time (measured in months) elapses during systemic and other therapies. The response to these treatments influences whether patients are still considered for surgery: non-responders and those progressing on treatment are less likely to have metastasectomy while those who respond well to treatment are more likely to have had surgery. Only after all treatments and evaluations are complete, and further passage of time for re-evaluation and consultation, did one among 37 patients in this analysis have a liver metastasectomy.[5] They are therefore a highly selected group of patients likely to have a better prognosis than the majority of patients with metastases.

Survival from diagnosis to metastasectomy, passing repeated assessments of prognosis, and appearing fit enough to undergo a further substantial treatment were requirements for a patient to have a liver metastasectomy and therefore be included in this line on the graph. The plateau at the beginning of the curve of the metastasectomy group, during which few patients died, is not a consequence of the metastasectomy; it is an extended form of immortal time bias.[12] This problem was understood by the analysts who included a landmark analysis to address it[5] and it is clear that these data should not be taken as evidence of a survival benefit from liver metastasectomy.

But careful explanations and caveats are not always possible during short presentations in clinical conferences. (Table 1) Importantly the beliefs of the speakers, most of whom are liver surgeons, may well have been aligned with this opening statement in another BJS paper: 'The surgical management of colorectal liver metastases (CRLMs) was a paradigm change in the management of metastatic disease and is one of the greatest advances in surgical practice of recent times.'[11] For liver surgeons, metastasectomy is the largest component of their work. Using this graph the speakers pointed out survival at five years as similar to that for patients who were stage III at the time of registration. In putting up this graph the inference drawn seemed to be that liver resection offers survival for metastasectomy patients; that appeared to be why they showed the graph.

With so much patient variation, selection and other treatment effects, a randomised trial is needed to detect a trustworthy treatment effect.[9;13] There is now some evidence from one randomised controlled trial (CLOCC) in which radiofrequency ablation (RFA) was used in patients not deemed suitable (at the time) for surgical resection. One arm was randomly assigned to have RFA to liver metastases while both arms had chemotherapy.[8] Overall survival over the first three years (the period contributing most to the inferred better survival in the 2010 BJS graph) was identical in the two arms of CLOCC and better than the notional survival against which claims for liver metastasectomy are made.

The opening line of the CLOCC trial report reads: 'Surgery is the gold standard of treatment in patients with resectable colorectal liver metastases'. But there is no good evidence to support this assertion and liver surgeons have consistently resisted a 'fair test' by random assignment for metastasectomy, asserting for example in 1995 '… any future demand for prospective trials on the general effectiveness of hepatic resection for metastatic colorectal cancer [is] not only obsolete but unethical'[14] and restating it more than twenty years later: 'On ethical grounds, a true randomised clinical trial comparing both treatment strategies in patients with resectable CRLM [colorectal liver metastases] has not been, and will not be performed'[15] In view of the importance of the question and the lack of evidence, should these strong statements of belief really prevent consideration of a 'fair test' by others? We are aware that there is a statement in the original paper 'patients are being denied access to a potentially curative treatment that could significantly improve their survival'[5] which goes beyond what one could conclude from the analysis itself. The words 'potentially' and 'could' offer some wriggle room, but the new information given here, and from the CLOCC trial, make the statement no longer valid. We offer in mitigation our concluding quotation which has a resonance: "When my information changes, I alter my conclusions. What do you do, sir?"[†]

[†] https://en.wikiquote.org/wiki/Talk:John_Maynard_Keynes

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