Surgical management and outcomes of colorectal cancer liver metastases

Eva Morris
Section of Epidemiology & Biostatistics (Institute of Cancer & Pathology (LICAP) and Institute of Data Analytics (LIDA)) Leeds, UK

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

*Corresponding author

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It is regrettable that the authors regard our paper as 'extremely personal'. That was never our intention. The original paper has been widely cited and others are using the graph.[1] Peer review asked for specific instances to add veracity to our statement - hence the inclusion of the table. Our published article has since been scrutinised independently by senior clinicians, patients, and by legal representatives for both the publisher and the University of Leeds. They accepted our paper as fair comment rather than a personal disagreement and have encouraged the conventional approach – an open exchange in the journal. We welcome, therefore, the opportunity to respond to the letter to the editor and to emphasise that our sole concern is that appropriate inferences are drawn from studies making use of routine NHS data in order to inform evidence-based care of patients with advanced colorectal cancer.

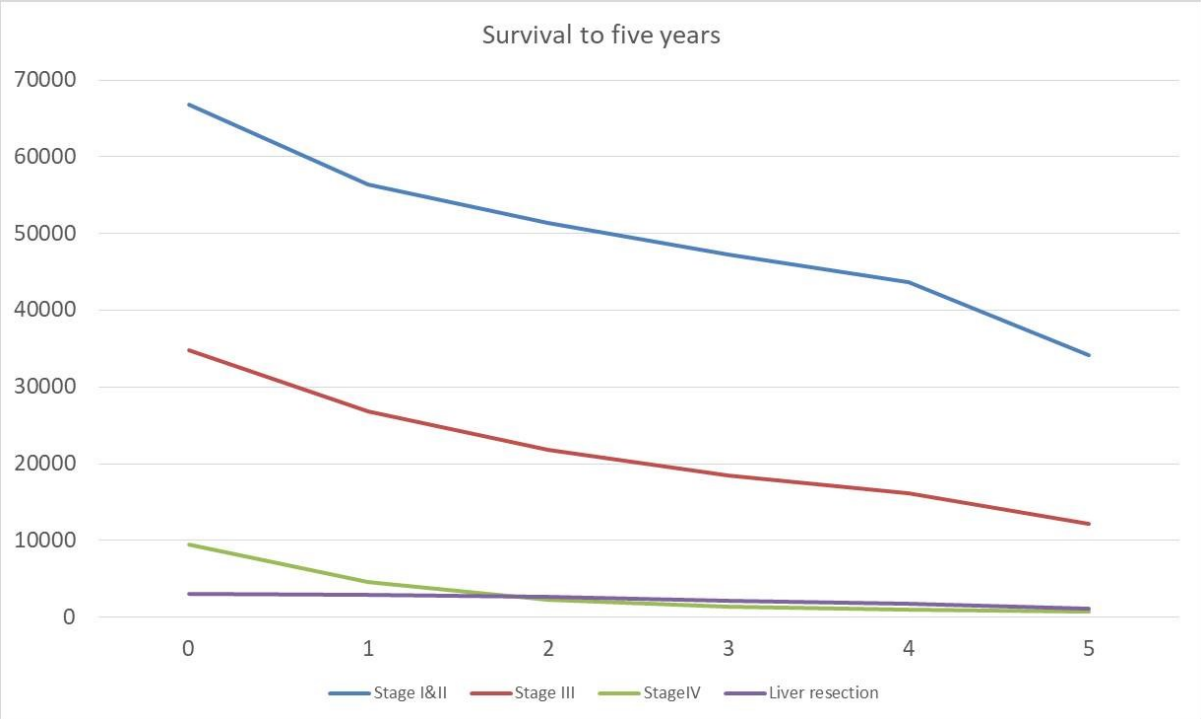
Contrary to what Fenwick and colleagues write, we did not assert "that a clinical practice cannot be adopted unless preceded by a successful prospective randomised clinical trial showing its benefit". On the contrary, it is self-evident that most established surgical interventions are based on observational evidence and there are plenty of instances where no one would countenance randomised trials. Where there is a clear mechanistic effect and a close temporal relationship between the intervention and the resolution of the clinical problem, whether that is survival or symptomatic relief, benefit may be evident without the need for controls.[2;3] For metastatic colorectal cancer, however, there is wide variation in extent of disease and its rate of progression. In addition, other treatments are used in sequence or conjunction and the contribution made by any one component cannot be reliably determined without control data.[4] There are many well documented examples where RCTs have shown accepted treatments to be ineffective.[5]

Randomised trials of interventions are particularly difficult to achieve[6] and the CLOCC trial cited by Fenwick has its limitations. The number of metastases is a powerful prognostic factor which would have had to be balanced between the groups to draw a trustworthy inference. Instead there was a clustering of patients with fewer metastases (1-3 metastases in 29/60 patients) in the group assigned to ablation while 33/59 patients in the control arm had five or more metastases. With only 11 patients in the analysis at 10 years this makes any conclusion vulnerable. CLOCC's real worth is that it shows that RCTs can be done in this difficult context - hence our belief that further and better trials should be undertaken into interventional treatments of metastases.

We return to the point of our paper. To make our message plainer we have plotted the actual numbers of patients from the original paper[1] and as reproduced in our recent paper.[7] With the actual numbers shown, it is striking how highly selected were the patients who had liver resections. Speakers at the 6th International Workshop on the treatment of Hepatic and Lung Metastases from Colorectal Carcinoma (Barcelona 16th and 17th November 2017) emphasised the importance of careful selection on the basis of known prognostic factors, the continuation of chemotherapy between staged procedures, and the importance of a deliberate delay - the 'test of time'- and to exclude patients whose disease is progressing. The addition of the 'test of time' results in immortal time bias. In the replotted data the resulting plateau can be discerned to last for about two years. Thereafter the line has a shallow downward trajectory very much like that of the Stage IV patients when the effect of immortal time bias has played out. It

would require random assignment to attribute any perceived difference in survival to liver resection.

There is no doubt that the progress made in liver resection is remarkable and the technical achievements speak to the dedication and technical ability of present day liver surgeons. A report of outcomes for liver-first surgery for colorectal cancer illustrates remarkable surgical achievement.[8] The presentation of "ALPPS" (associating liver partition and portal vein ligation for staged hepatectomy) in Barcelona left not only the oncologists but their surgical colleagues in awe.[9] However as the practitioners of these advanced techniques seek to widen the scope of liver surgery, it seems reasonable to consider for how many patients survival is better than would have been achieved by systemic treatments in similarly selected patients.[4] We believe that strong research evidence is vital to deliver this ambition and our only intention was to generate discussion about how robust the observational data might be. As Fenwick and colleagues state, collaborative working is required to make the advances in the care of colorectal cancer patients that we all seek.



Legend
The data from the original paper[1] and our reconsideration of its conclusions[7] have been plotted as the actual numbers surviving annually up to five years.

Reference List

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