

Research Letter

Pulmonary Metastasectomy in Colorectal Cancer: the PulMiCC randomised controlled trial.

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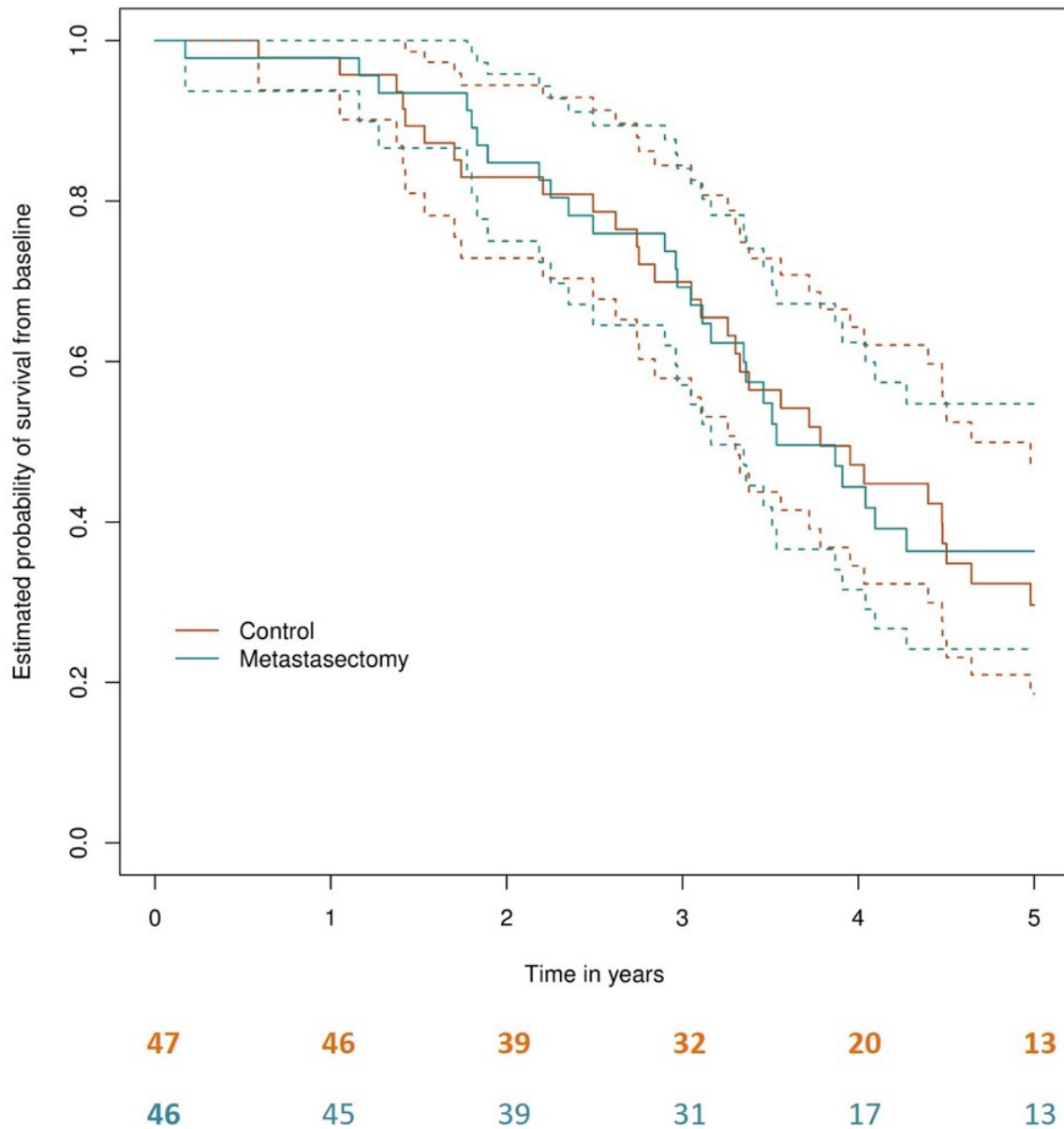
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The randomised controlled trial, Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) was discussed in BJS early in its course(1) and has now been published.(2) We are pleased to have this opportunity to return to the BJS with our findings. Of 93 randomised patients, the 46 assigned to lung metastasectomy survived for a median of 3.5 years while 47 who had no metastasectomy lived a median of 3.8 years. As can be seen, the survival curves did not separate. (Figure) At four years, survival was 44% (95%CI:29%-61%) for patients assigned to metastasectomy, similar to the many surgical follow-up studies. In the control arm it was 47% (95%CI:32%-63%). Importantly, no control patients crossed over to have metastasectomy or any form of ablation, as the initial treatment for their lung metastases.

Members of the Guideline Committee have summarised NICE guidance on surgery for colorectal cancer metastases.(3) PulMiCC was discounted by them because of the 'small sample size'. The justification given was that the PulMiCC trial did not reach its target recruitment and was therefore 'underpowered'. This is an irrelevant argument when analyzing available data. It is generally believed that five-year survival without metastasectomy is zero.(4) Even if it was 5%, the expected PulMiCC results would be 3/47 versus 18/46, $P < 0.0002$ by Fisher's test. Would that result be ignored on the basis of small numbers? More generally, under this scenario, the power of PulMiCC, as recruited, would have been 99% but the PulMiCC team knew from a modelling study, that a near zero-assumption was far from the truth. A higher target number was set for the relevant, but more difficult proof of non-inferiority. For any future trial, the power calculation would have to take into account these trial data, as should guidance on clinical practice. The PulMiCC trial was meticulously carried out, with balance in the trial arms achieved. It was independently monitored and analysed, with blinding of all members of the trial management group until after analysis.

Having set PulMiCC aside, the Guideline Committee used for their evidence a retrospective analysis.(5) While the RCT's 46 randomised metastasectomy patients were too few to consider, the study they relied on had 48 highly selected patients. Unless the prime number 47 has some special threshold significance, this suggests that there is not really a sufficient, or indeed, credible reason to set aside the only RCT available. In this analysis of a selective practice, a comparison was made with 57 patients who had been turned down for metastasectomy, precisely because they had much higher rates of the well-established negative prognostic features: more metastases, more lobes involved, bilateral lung involvement, additional liver metastases, elevated carcino-embryonic antigen, and shorter intervals since primary resection. Of course, this was a retrospective study so it was also *already known* that all 57 had died within five years.

The reason that PulMiCC was not larger was a combination of participating thoracic surgeons' convictions that without lung metastasectomy none of these patients would survive, and external pressure on them to fall in line with accepted practice in the management of metastatic colorectal cancer. As a result, of 512 patients who gave consent to enter the study, only 18% were eventually randomised. Among 155 eligible patients who had not been randomised in the three largest recruiting centres, we identified 41 patients who wanted to make their own decision. The split was 22:19, to have or not have metastasectomy. Among 78 patients in whom the clinical team overrode the patients' willingness to be randomised, 77 (99%) were operated on. The patients exhibited group equipoise, whereas the clinicians, when it came to it, found themselves unable to.



Legend for the Figure

The Kaplan Meier analysis for the PulMiCC trial. Reproduce with permission Figure 3 in Milosevic M, Edwards J, Tsang D, Dunning J, Shackcloth M, Batchelor T, et al. Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. *Colorectal Disease*. 2020 (2). It is reproduced with permission from Wiley. This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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