

Pulmonary metastasectomy in colorectal cancer (PulMiCC). Assumed benefits are not confirmed by new study findings.

Response to Pilozzi E. Histological growth patterns and molecular analysis of resected colorectal lung metastases. 2021.

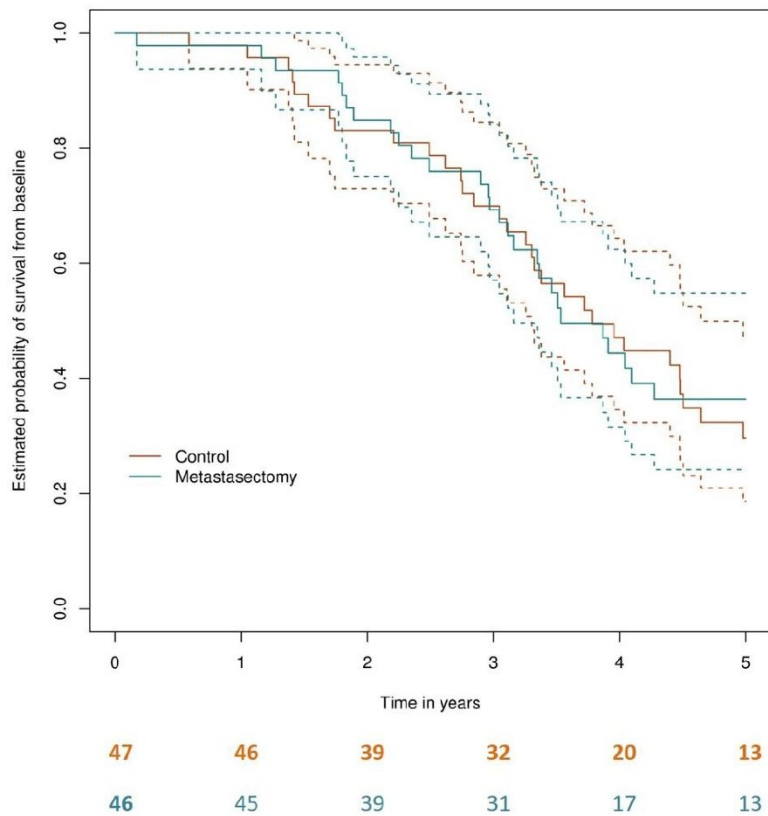
Tom Treasure MD MS FRCS FRCP

Clinical Operational Research Unit, University College London, UK

Contact: [tom.treasure@gmail.com](mailto:tom.treasure@gmail.com)

The author has no conflict of interest to declare.

PulMiCC was funded by Cancer Research UK Grant No. C7678/A11393



Dear Editor

As Chief Investigator of the PulMiCC study (Pulmonary Metastasectomy in Colorectal Cancer) I thank Dr Pillozzi and colleagues for referring to our study among others in their elegant and detailed work on colorectal lung metastases[1]. In their introduction they restate the generally accepted view that lung metastasectomy improves survival but they also recognise that this has been put into question by recent reports.[2, 3]

The full PulMiCC multicentre cohort of 512 patients has now been published[4]. Nested within it was the PulMiCC randomised controlled trial (RCT) in 93 patients for whom survival[3], quality of life[2], and health utility[5] have been published. There was no significant difference in survival at any time point. (Figure) We cannot exclude the possibility that there is a difference emerging with longer follow up but it cannot be nearly as great as has been generally accepted. This conclusion is supported by a “big data” analysis of 10,325 patients in the Surveillance, Epidemiology and End Results (SEER) database[6].

If PulMiCC RCT results seem surprising we should pause to reconsider the low quality of evidence that has been relied on for lung metastasectomy to become a standard therapy. Survival without metastasectomy was assumed be “zero” in a *consensus* statement published in the journal of the Society of Thoracic Surgeons (STS) but the authors admitted that no control data had ever been reported[7]. In an editorial in the journal of the European Society of Thoracic Surgeons (ESTS) survival after lung metastasectomy was reported as 60% by selective citation of a couple of follow-up studies[8].

With a claimed margin of benefit of that magnitude, randomisation within the PulMiCC cohort study was difficult and the nested RCT randomised 93, fewer than one patient in five. Meanwhile the cohort of well characterised and prospectively collected patients grew. Multidisciplinary teams in 25 trial sites selected 263 of the non-randomised patients to have lung metastasectomy. Their five-year survival was 47% which was in line with “real world” results in a meta-analysis of 2,925 patients.[9] But survival among 128 non-operated patients was far higher than had ever been suggested at 22%.[4] The more than two-fold difference in survival rates was explicable by the expert and well-informed selection of patients for operation. Metastasectomy patients had predominately solitary metastases, lower rates of liver involvement, and fewer had elevated carcinoembryonic antigen. They also had better ECOG score profiles and better lung function.[4]

In contrast, in the RCT the metastasectomy and control arms were very well balanced. After an initial grace period with few deaths—which is a characteristic of cancer trials—the lines weave in and out of each other. (Figure)

Clinicians caring for patients with CRC metastases will increasingly value insights into cancer biology of the kind reported by Pillozzi et al but it is important to know that metastasectomy itself gives little if any benefit to the patients. CRC lung metastases are asymptomatic and the lethal disease is nearly always elsewhere. Put together the control data in the PulMiCC cohort, the “big data” analysis, and the RCT indicate that lung metastasectomy provides little or no survival or quality of life benefit for these patients.

## References

- [1] E. Pillozzi, Histological growth patterns and molecular analysis of resected colorectal lung metastases, (2021).
- [2] T. Treasure, V. Farewell, F. Macbeth, K. Monson, N.R. Williams, C. Brew-Graves, B. Lees, O. Grigg, L. Fallowfield, Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial, *Trials* 20(1) (2019) 718.
- [3] M. Milosevic, J. Edwards, D. Tsang, J. Dunning, M. Shackcloth, T. Batchelor, A. Coonar, J. Hasan, B. Davidson, A. Marchbank, S. Grumett, N.R. Williams, F. Macbeth, V. Farewell, T. Treasure, Pulmonary Metastasectomy in Colorectal Cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed, *Colorectal Dis* 22(10) (2020) 1314-1324.
- [4] T. Treasure, V. Farewell, F. Macbeth, T. Batchelor, M. Milosevic, J. King, J. Zheng, P. Leonard, N. Williams, C. Brew-Graves, L. Fallowfield, Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) Cohort Study: analysis of case selection, risk factors and survival in a prospective observational study of 512 patients., *Colorectal Disease* (IN PRESS) (2021).
- [5] C. Brew-Graves, V. Farewell, K. Monson, M. Milosevic, N. Williams, E. Morris, F. Macbeth, T. Treasure, L. Fallowfield, Pulmonary Metastasectomy in Colorectal Cancer: Health Utility scores by EQ-5D-3L in a randomised controlled trial show no benefit from lung metastasectomy, *Colorectal Disease* 23(1) (2021) 200-205.
- [6] A.R. Siebenhuner, U. Guller, R. Warschkow, Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases, *BMC Cancer* 20(1) (2020) 246.
- [7] J.R. Handy, R.M. Bremner, T.S. Crocenzi, F.C. Detterbeck, H.C. Fernando, P.M. Fidas, S. Firestone, C.A. Johnstone, M. Lanuti, V.R. Litle, K.A. Kesler, J.D. Mitchell, H.I. Pass, H.J. Ross, T.K. Varghese, Expert Consensus Document on Pulmonary Metastasectomy, *Ann. Thorac Surg* 107(2) (2019) 631-649.
- [8] J. Schirren, M. Schirren, L. Lampl, S. Sponholz, Editorial. Surgery for pulmonary metastases: quo vadis?, *Eur. J Cardiothorac. Surg* 51(3) (2017) 408-410.
- [9] M. Gonzalez, A. Poncet, C. Combescure, J. Robert, H.B. Ris, P. Gervaz, Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis, *Ann. Surg. Oncol* 20(2) (2013) 572-579.