https://doi.org/10.1590/1806-9282.20211094

# The Pulmonary Metastasectomy in Colorectal Cancer study calls for reconsideration of the clinical effectiveness of this widespread practice

Tom Treasure[1*], Fergus Macbeth[2], Riad Younes[3]

Dear Editor,

We read with great interest the report by Dr. Oya Yildiz and colleagues on pulmonary metastasectomy for patients with colorectal cancer (CRC)[1]. The authors make brief reference to the preliminary results of the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial[2], which drew our attention to their report. The randomized controlled trial (RCT) was nested within a cohort study of 512 patients, which has now been reported in full as has the completed RCT[3,4]. We believe that the findings of the full PulMiCC study are directly relevant to the interpretation of their findings.

While the PulMiCC study was ongoing, the authors worked together in the Surgical and Interventional Trials Unit (SITU) at University College London on a meta-analysis of monitoring protocols following resection of primary CRC[5]. There were 16 randomized trials, of which 11 provided data suitable for meta-analysis. The purpose of these monitoring protocols is to detect relapse, and particularly metastatic disease, with the intention of increasing the numbers of patients suitable for metastasectomy. They were successful in advancing the diagnosis by a median of 10 months (IQR 5–24), but there was no survival gain. A Cochrane meta-analysis provided similar conclusions[6].

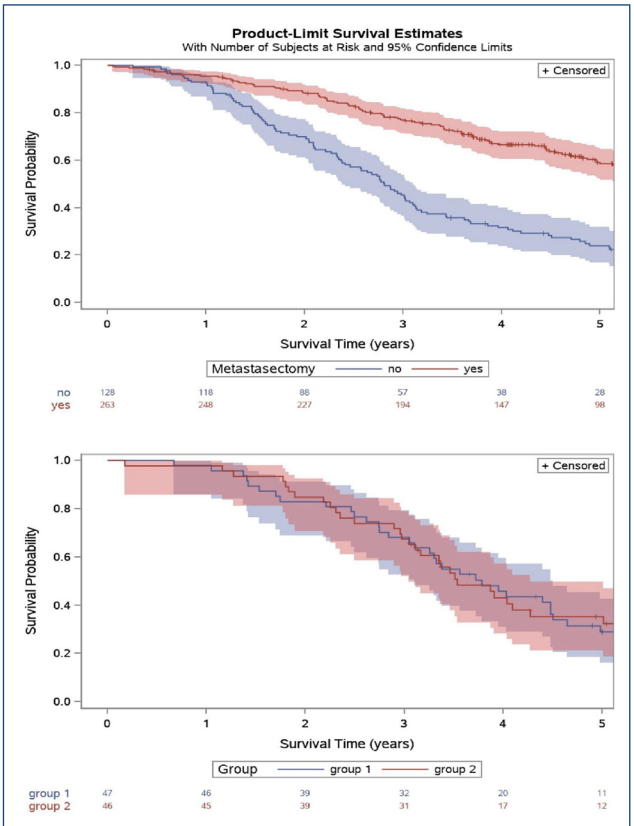
The meta-analysis raised doubts about the assumed survival benefit of CRC lung metastasectomy, which has become the standard of care internationally. It was said to be "a pillar of modern thoracic surgery" in an Editorial in the *European Journal of Cardio-Thoracic Surgery* (*EJCTS*)[7]. Two observational studies of metastatic CRC (mCRC) were cited with a pooled 5-year survival of 60%. And then, in the United States, the Society of Thoracic Surgeons (STS) in an Expert Consensus Document reported that "survival is assumed to be zero" in patients with lung metastases[8]. The gap between these figures — 60% versus zero — was considered to be the effect attributable to lung metastasectomy.

In the full PulMiCC study, 512 patients gave informed consent to be considered for lung metastasectomy and baseline data were collected according to RCT standards. Of them, 28 were excluded because — during initial evaluation — their nodules were found to not be CRC metastases. Because of the widely held belief in the 60% increase in 5-year survival, the clinicians' stated equipoise was challenged and only 93 patients were randomized. Of the remainder, 263 underwent metastasectomy and 128 were not operated, comprising 391 patients in the nonrandomized cohort. The survival of these two groups is illustrated in the Kaplan-Meier analysis in the upper panel of the (Figure 1). The operated patients had a survival of about 60% in line with the best reported series cited in the *EJCTS* editorial[7]. But the survival of patients selected to *not* have an operation was not zero contrary to the STS consensus[8].

The data collected at baseline under trial conditions permitted a full analysis of the features of the patients in the electively operated and unoperated groups. These data were of course used in making these elective decisions. The operated group was dominated by solitary metastases (69% vs. 35%) and far fewer had more than five metastases (0.8% vs. 10.3%). There were also fewer patients with hepatic involvement (28% vs. 36%) and fewer with elevated carcinoembryonic antigen levels (12% vs. 20%). They were younger (60 vs. 67 years), more had unimpaired performance (68% vs. 36% using Eastern Co-operative Oncology Group scores), and they had better lung function (predicted $FEV_1$ 96% vs. 87%). All of these factors favored

[1]University College London, Clinical Operational Research Unit – London, United Kingdom.
[2]Cardiff University, Centre for Trials Research – Cardiff, United Kingdom.
[3]Hospital Alemão Oswaldo Cruz, Cancer Center – São Paulo (SP), Brazil.
*Corresponding author: tom.treasure@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on November 03, 2021. Accepted on December 24, 2021.




AQ: Please check and/or provide a suitable figure caption.

**Figure 1.** Five-year survival estimates of patients at risk.

better survival in patients having metastasectomy irrespective of subsequent treatment[4].

To know how much of a difference was actually attributable to lung metastasectomy required randomized control data, shown in the lower panel of the figures. These factors were excellently balanced in the two arms of the randomized trial. The two curves were weaving in and out of each other. The median survival was longer in the control group (45.6 months vs. 42.0 months), but there was no difference in survival at any time point. Estimating the possible difference in survival at 5 years is precluded by the broad confidence bands around the arms of 46 and 47 patients, but it cannot be anything like the magnitude believed. It is also important to know that in the RCT, the performance status diminished at a similar rate in the two groups, there was no psychological benefit, and that there was a relative loss of lung function in the operated patients. There was no benefit but demonstrable harm.

An inescapable feature of the clinical care of these patients is that time elapses between when they are first identified and when the operation is actually carried out. Patients who progress during this time, either in the lung or at other sites, are less likely to have an operation and so those eventually selected are unlikely to die in the next year or so. This introduces guarantee time bias[9]. A "guarantee time" also applies in RCTs, but it affects both arms. Provided the report is on intention to treat and from time of randomization (as it should be), this eliminates the bias.

The report of Yildiz et al. is exceptional in that they provide information about the denominator from which their patients were drawn in contrast to the publications in the systematic review[10]. Yildiz et al. reported that 33 patients who had lung metastasectomy were among 607 patients treated for mCRC in their center (5.4%, 95% confidence intervals 3.8–7.6%). From English National Health Service data (2005–2013), we estimate that 4.9% of about 70,000 patients with mCRC had pulmonary metastasectomy, a very similar figure. The degree of case selection is closely comparable.

The PulMiCC cohort also provides data on further treatments[11]. Yildiz et al. draw the following conclusion from their experience: "Therefore, we have to make a vigilant follow-up for the second lung relapse to seize an opportunity for the second metastasectomy[1]." The PulMiCC analysis of additional treatments cannot refute the belief that there is benefit from repeat metastasectomy because there was no controlled comparison, but on statistical review of the claims, it seems unlikely[12,13]. Also reported from PulMiCC are the quality of life, health utility, and the burden of additional treatments[3,11,14]. Given the low likelihood of survival benefit in the PulMiCC RCT[3], it seems difficult to justify these treatment burdens.

Yildiz and colleagues are very realistic about the limitations of their small study.

The surgical treatment of metastatic disease has grown, and belief in its effectiveness is sustained by expert case selection of those naturally most likely to survive. This is compounded by guarantee time bias, confusing association with causation, affirmation bias, and remarkable optimism. It is perhaps time for realism and a more careful appraisal of the evidence, which currently does not support the belief in a substantial survival benefit. Recent reports, including rebuttals of the PulMiCC RCT findings, suggest that the new objective of treatment is local control rather than "cure," but this is "moving the goal posts." Few patients experience symptoms from isolated lung metastases and so local control is not an important clinical issue. For systemic treatments, it is accepted that no drug should be introduced without RCT evidence and the same should be true for local interventions[15]. Sufficiently large, collaborative, and independently monitored controlled trials are needed. PulMiCC illustrates the difficulties encountered but also shows an approach to planning such trials[16].

## REFERENCES


1. Yildiz O, Dae S, Findkcioglu A, Kose F. Survival outcome of pulmonary metastasectomy among the patients with colorectal cancers. Rev Assoc Med Bras. 2021;67(7):1015-20. https://doi.org/10.1590/1806-9282.20210472
2. Treasure T, Farewell V, Macbeth F, Monson K, Williams NR, Brew-Graves C, et al. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. Trials. 2019;20(1):718. https://doi.org/10.1186/s13063-019-3837-y
3. 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 Dis. 2020;22(10):1314-24. https://doi.org/10.1111/codi.15113
4. Treasure T, Farewell V, Macbeth F, Batchelor T, Milošević M, King J, et al. The Pulmonary Metastasectomy in Colorectal Cancer cohort study: analysis of case selection, risk factors and survival in a prospective observational study of 512 patients. Colorectal Dis. 2021;23(7):1793-803. https://doi.org/10.1111/codi.15651
5. Mokhles MM, Kortke H, Stierle U, Wagner O, Charitos EI, Bogers AJJC, et al. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation. 2011;123(1):31-8. https://doi.org/10.1161/CIRCULATIONAHA.110.947341
6. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2016;9(9):CD002200. https://doi.org/10.1002/14651858.CD002200.pub4
7. Schirren J, Schirren M, Lampl L, Sponholz S. Editorial. Surgery for pulmonary metastases: quo vadis? Eur J Cardiothorac Surg. 2017;51(3):408-10. https://doi.org/10.1002/14651858.CD002200.pub4
8. Handy JR, Bremner RM, Crocenzi TS, Detterbeck FC, Fernando HC, Fidias PM, et al. Expert Consensus Document on Pulmonary Metastasectomy. Ann Thorac Surg. 2019;107(2):631-49. https://doi.org/10.1016/j.athoracsur.2018.10.028
9. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31(23):2963-9. https://doi.org/10.1200/JCO.2013.49.5283
10. Fiorentino F, Hunt I, Teoh K, Treasure T, Utley M. Pulmonary metastasectomy in colorectal cancer: a systematic review and quantitative synthesis. J R Soc Med. 2010;103(2):60-6. https://doi.org/10.1258/jrsm.2009.090299
11. Treasure T, Farewell V, Macbeth F, Batchelor T, Milosevic M, King J, et al. The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) burden of care study: analysis of local treatments for lung metastases and systemic chemotherapy in 220 patients in the PulMiCC cohort. Colorectal Dis. 2021;23(11):2911-22. https://doi.org/10.1111/codi.15833
12. Treasure T, Mineo T, Ambrogi V, Fiorentino F. Survival is higher after repeat lung metastasectomy than after a first metastasectomy: too good to be true? J Thorac Cardiovasc Surg. 2015;149(5):1249-52. https://doi.org/10.1016/j.jtcvs.2015.01.067
13. Fiorentino F, Treasure T. Is survival really better after repeated lung metastasectomy? Clin Exp Metastasis. 2021;38(1):73-5. https://doi.org/10.1007/s10585-020-10061-z
14. Brew-Graves C, Farewell V, Monson K, Milošević M, Williams NR, Morris E, et al. Pulmonary metastasectomy in colorectal cancer: health utility scores by EQ-5D-3L in a randomized controlled trial show no benefit from lung metastasectomy. Colorectal Dis. 2021;23(1):200-5. https://doi.org/10.1111/codi.15386
15. Jawed I, Wilkerson J, Prasad V, Duffy AG, Fojo T. Colorectal cancer survival gains and novel treatment regimens: a systematic review and analysis. JAMA Oncol. 2015;1(6):787-95. https://doi.org/10.1001/jamaoncol.2015.1790
16. Fiorentino F, Treasure T. Sample size calculations for randomized controlled trials and for prediction models. Colorectal Dis. 2021;23(1):316-9. https://doi.org/10.1111/codi.15489