Title

A well balanced randomised controlled trial in 93 patients is more trustworthy than attempted propensity matching in 38 patients: comments on Schlachtenberger et al.

Mišel Milošević MD Thoracic Surgeon Thoracic Surgery Clinic, Institute for Lung Diseases of Vojvodina, Sremska Kamenica, Serbia

Tom Treasure MD*
Professor of Cardiothoracic Surgery
Clinical Operational Research Unit, University College London, London, UK

Francesca Fiorentino Senior Lecturer in Statistics King's College London, UK

*Corresponding author Tom Treasure

Address: Clinical Operational Research Unit 4 Taviton Street London WC1H0BT

No fax E-mail tom.treasure@gmail.com Telephone 00 44 7957 168754

None of the authors has a conflict of interest to declare

Word count 496

We were interested in the propensity score-matched analysis of head and neck cancer metastasised to the lung undertaken to "further clarify that PM prolonged survival." The method for propensity score matching is not described. (1) The authors list the matching factors, but not the statistical method used for the matching, hence it is difficult to comment on whether the matching was done appropriately. But from what is described there are several points in the paper which suggest that the number of patients available was too small. For logistic regression, integral to propensity matching, the rule of thumb is that you need 10 patients per factor to be matched. Table 4 lists 14 factors, too many for a comparison of 19 vs 19 patients. The text refers to Student's *t*-test to compare the groups but it is a test of significant *difference*, not similarity. McNemar test is used for *paired* data, for example to compare repeated measurements in the *same* patient.

We were defeated in our own attempt to use propensity matching for colorectal (CRC) lung metastases so we sincerely sympathise with the authors and regret the unavoidable statistical quibbling. One of us (MM) had a personal series of 73 well documented colorectal cancer (CRC) patients 2004-2012 and was granted access to data on 20,006 patients in the Registry of Cancer in Central Serbia. We made a determined attempt but we did not trust the matches mainly because too few of the clinical factors could be matched in the registry. Siebenhuner and colleagues had more success. In the SEER database they found 807 patients with lung only CRC metastases and 1323 with liver and lung with no survival benefit.(2)

When there are no controlled studies a good propensity score matching analysis is a useful step. We appreciate Dr Schlatenberger and colleagues making reference to the pulmonary metastasectomy in colorectal cancer (PuMiCC) study which in fact recruited well with 512 patients giving written informed consent and providing baseline data of trial quality.(3) These provided a prospective cohort of 391 patients. The clinical teams chose 263 for metastasectomy with 60% five-year survival comparable with the best reported "real world" data and gave face validity to the PulMiCC cohort. The 128 whom they elected to not operate on had 22% survival, not the zero assumed in the STS Expert Consensus Document.(4) The chosen patients had better prognostic factors, often by a wide margin. The nested RCT 93 patients were excellently balanced for all prognostic factors — primary stage, number of metastases, carcinoembryonic antigen, interval since primary resection, liver involvement, age, performance status and lung function — and there was no difference in survival.(3) PulMiCC did not have statistical power to prove noninferiority but any benefit is very much smaller than is widely believed. (5) Where there is an RCT it is more reliable than attempts at matching but when the numbers were large enough the two methods were in accordance.(2) At least for colorectal cancer, a large benefit from lung metastasectomy is in doubt.(6)

References

- 1. Schlachtenberger G, Doerr F, Menghesha H, Heldwein MB, Lauinger P, Wolber P, et al. Pulmonary metastasectomy for metastatic head and neck cancer prolongs survival significantly compared to non-surgical therapy. Eur J Cardiothorac Surg. 2022.
- 2. Siebenhuner AR, Guller U, Warschkow R. Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases. BMC Cancer. 2020;20(1):246.
- 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.
- 4. 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.
- 5. Fiorentino F, Treasure T. Sample size calculations for randomized controlled trials and for prediction models. Colorectal Dis. 2021;23(1):316-9.
- 6. Macbeth F, Treasure T. The Biology and Systemic Treatments Influence Survival in Advanced Gastrointestinal Cancers While the Controlled Trial of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) Found That Surgical Resection Could Only Have a Small If Any Effect. Am J Clin Oncol. 2022;45(3):135-6.