

Title Page

The belief in clinical benefit from lung metastasectomy in colorectal cancer is questioned by the PulMiCC study and its nested randomised controlled trial.

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Text 575 words

In presenting their retrospective cohort of patients with colorectal lung metastases Denz et al recognise that “the usefulness of lung metastasis resection is being questioned”. (1) They go on to write “This is fueled by the recently published randomized controlled PulMiCC trial, which failed to show a benefit from pulmonary metastasectomy”. However, they give no details of the study design, the data and do not offer an interpretation. We are grateful to the editor for allowing us to present the salient points of our study. (2, 3) [Figure]

In PulMiCC (pulmonary metastasectomy in colorectal cancer) patients were recruited at 25 clinical sites. A cohort of 391 were managed as decided by the local team and of them 263 (67%) were selected for metastasectomy. They had better survival than the 128 not selected. (2) (Upper panel) Because clinical and oncological factors associated with longer survival were collected prospectively, to RCT standards, we were able to estimate that the survival difference might be fully explicable by the differences in these risk factors.

At 14 of the centres the treatment of 93 patients was assigned either to have metastasectomy or not by off-site randomisation with computerised balancing of the collected risk factors. (4) They form the PulMiCC RCT. (Lower panel) There was no evident difference in survival. The trial was powered to show “non-inferiority”. If operation provided a survival benefit, it can only be by a very small amount.

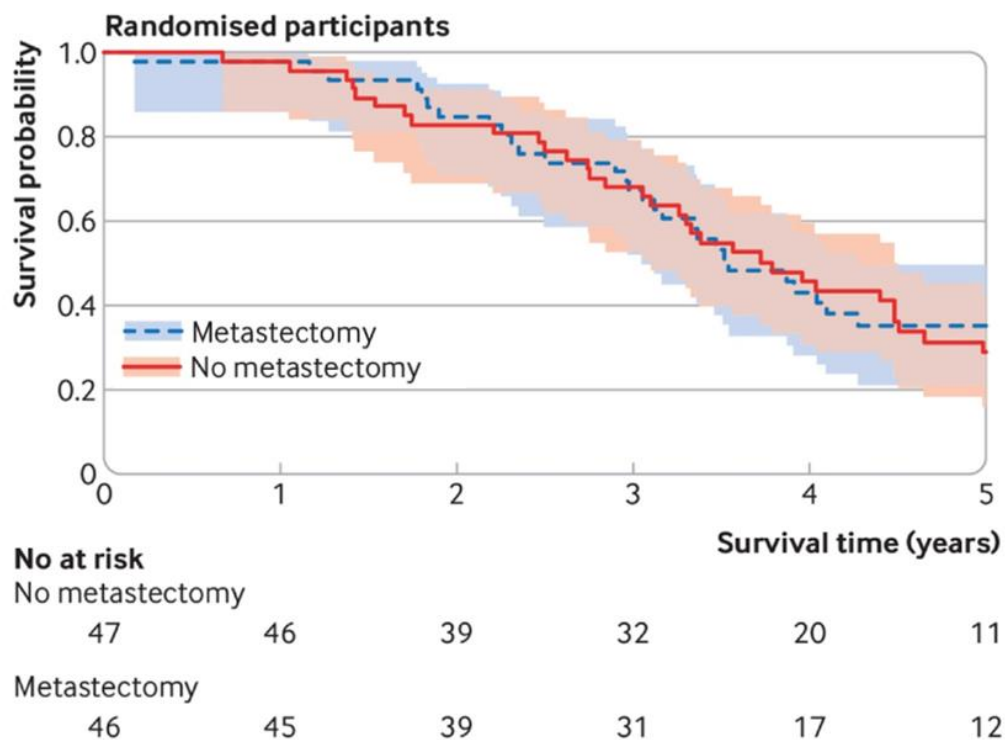
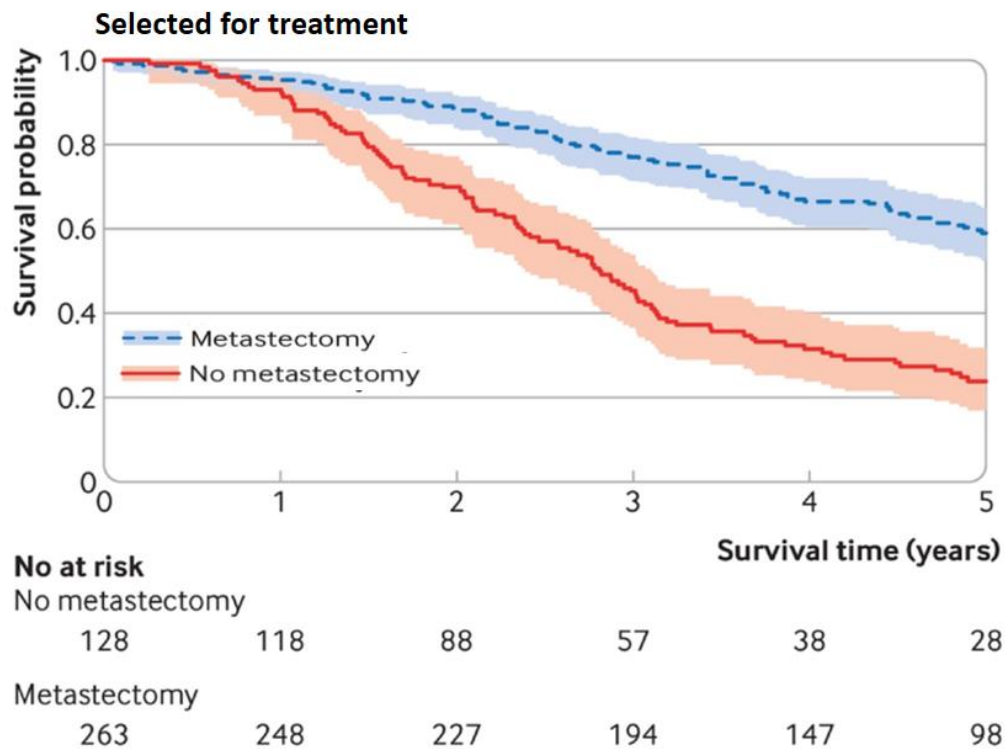
The Erlangen data show significant differences in the proportion of patients with the important prognostic factors for survival between the operated and non-operated groups. We believe that this, not the surgical intervention, could account for most if not all of the difference in survival.

It has been generally assumed that 5-year survival *without* lung metastasectomy would be zero. The Erlangen and PulMiCC data show that is not the case. There are a total of 290 patients (115, 128 and 47) whose metastases were not resected in the three survival comparisons. Reading from the curves and pooling the data the unoperated five-year survival is about 26%.

Also, there were few deaths among the Erlangen metastasectomy patients in the first two years. Two forms of bias are in play. The plot starts at the *appearance* of the metastases which would have been before the decision to operate and the operation itself. That is lead time bias. There is also time spent in assessment so that patients with any likelihood of dying within, say, a year are excluded by the process. Although reasonable exercise of clinical judgement, it results in guarantee-time bias.(5) It is seen in both arms of PulMiCC RCT (lower panel) but as the start time is from randomisation

in *both* arms it does not bias the interpretation and provides an intention to treat analysis.

The absence of any data on adverse events is presumably because this is difficult to retrieve in a retrospective study. The multivariate analysis showed an association between surgery and longer survival but that is only an *association* and other selection factors, unknown or unaccounted for, will have influenced the outcomes. Although Denz et al suggest that selection bias may have a role in their results they nevertheless conclude that their study “confirms the importance of surgical management” of patients with lung metastases. We disagree and believe that this study, like so many other uncontrolled retrospective series, is misleading. They say that “randomized trials are needed” but we know that they have no intention of doing one (Personal Communication MB) so it would seem reasonable to pay attention to RCT findings that exist..



Legend for the figure.

A prospective study of colorectal cancer patients treated with and without lung metastasectomy by clinical decision (above) or randomly assigned (below).

References

1. Denz A, Hahn V, Weber K, Weber GF, Grutzmann R, Krautz C, et al. Survival outcome following surgical versus non-surgical treatment of colorectal lung metastasis-a retrospective cohort study. *Langenbecks Arch Surg*. 2024;409(1):121.
2. Treasure T, Farewell V, Macbeth F, Batchelor T, Milosevic 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.
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.
4. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31(1):103-15.
5. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol*. 2013;31(23):2963-9.