Pulmonary metastasectomy: association is not causation. Response to Dudek et al.

Abstract (85 words)

The PulMiCC study, comprised a 512 patient cohort and a nested randomised controlled trial (RCT) in 93 patients. An observational study by Dudek and colleagues is reported to show an association between better survival and pulmonary metastasectomy but implicit in the presentation is an assumption of causation. The PulMiCC cohort included prospective baseline data of trial quality and taken together the results of the nested RCT indicates that if there is any survival benefit from pulmonary metastasectomy, it is far smaller than is generally believed.

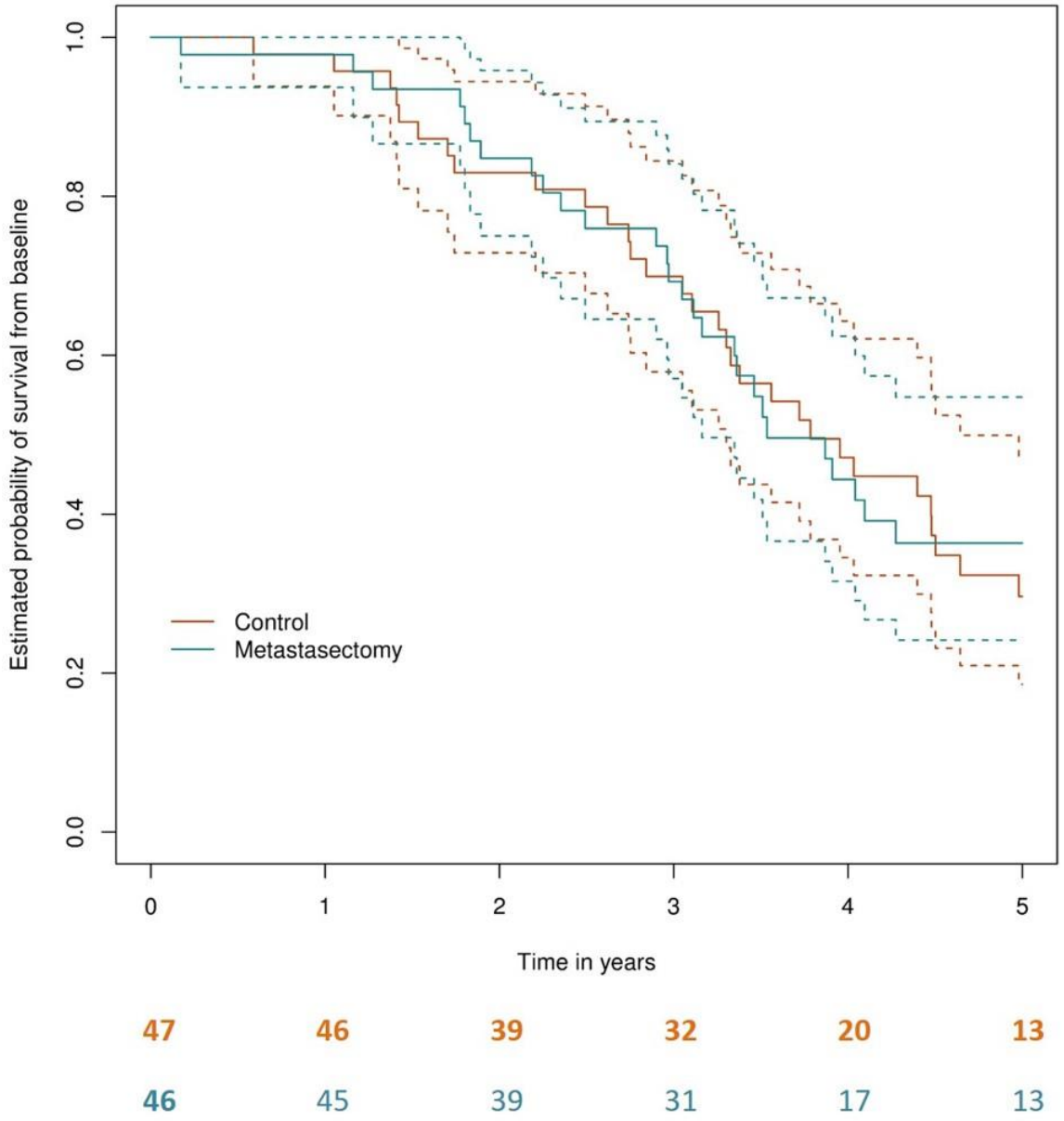
Text (465 words)

The recent paper by Dudek and colleagues (1) reports a retrospective institutional case series of patients who had undergone pulmonary metastasectomy (PM) for a wide variety of tumours. It is a comparatively large series, providing a wealth of detail, and the overall survival results (47.1% at 5 years) are claimed to be due to the surgical intervention. They state: 'The use of PM as a part of multimodal treatment is in (a) selected population justified'. This conclusion is misleading because without a comparable unoperated control group the apparently favourable outcome could be largely or entirely the result of the selection process alone. Without good evidence of benefit the risks of surgery, however low, may not be justified.

They kindly cite our report of PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer), the only randomised controlled trial (RCT) that has addressed this question. As they say, it closed early with 93 patients randomised.(2) But it was nested within a cohort of 512 patients(3) and to fully understand the results, both should be considered. In the cohort 263 patients with lung metastases from colorectal cancer had PM. Five-year survival was 47% (the same as Dudek's) compared with 22% among 128 patients not who did not have PM. Patients selected for metastasectomy had better ECOG scores and % predicted FEV1, while fewer had elevated CEA or a history of liver metastasectomy. Notably 65% had a solitary metastasis compared 31% in the patients selected to not have PM. The differences in prognostic factors could easily explain the survival difference. In contrast, the two arms of the RCT were very well balanced for all prognostic factors. There was no difference in survival at any time point. (Figure) We cannot exclude an eventual small benefit but the widely believed survival difference of 40-50% is precluded by the survival rates of non-PM patients in both the large cohort study and the RCT.

Dudek et al imply that because PulMiCC failed to recruit fully, further RCTs are unlikely to succeed. Unfortunately, that may well be correct unless clinicians allow themselves the possibility of doubt, but they are wrong to say that a 'well-designed large multicenter cohort study including a control group… could also efficiently (*assess*) the value of the PM for particular types of metastatic cancer.' Even if it were possible to find such a control group balanced for known prognostic factors, unrecorded confounding factors would always make such a study misleading.

Their final conclusion is: 'Our 10-year single-center experience demonstrates that PM is associated with long-term survival benefits.' An association has indeed been shown. But association is not evidence of causation and this study provides no new evidence to support the very widespread but as yet unproven belief that PM has a major effect on the survival of the patients to whom it is recommended.



Legend to figure

Kaplan Meier analysis of PulMiCC. There are few deaths in either group in the first 1-2 years. This typical of RCT results due to guarantee time bias inherent in prospective studies. Thereafter the curves weave in and out of each other. There is no significant difference at any time. Median survival was longer in the controls at 3.8 years compared with 3.5 in the PM arm.

References

1. Dudek W, Schreiner W, Haj Khalaf M, Sirbu H. Surgery for Pulmonary Metastases: Long-Term Survival in 281 Patients. Thorac Cardiovasc Surg. 2021.
2. 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.
3. Treasure T, Farewell V, Macbeth F, Batchelor T, Milosevic M, King J, et al. 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 Dis. 2021.