

Observations on

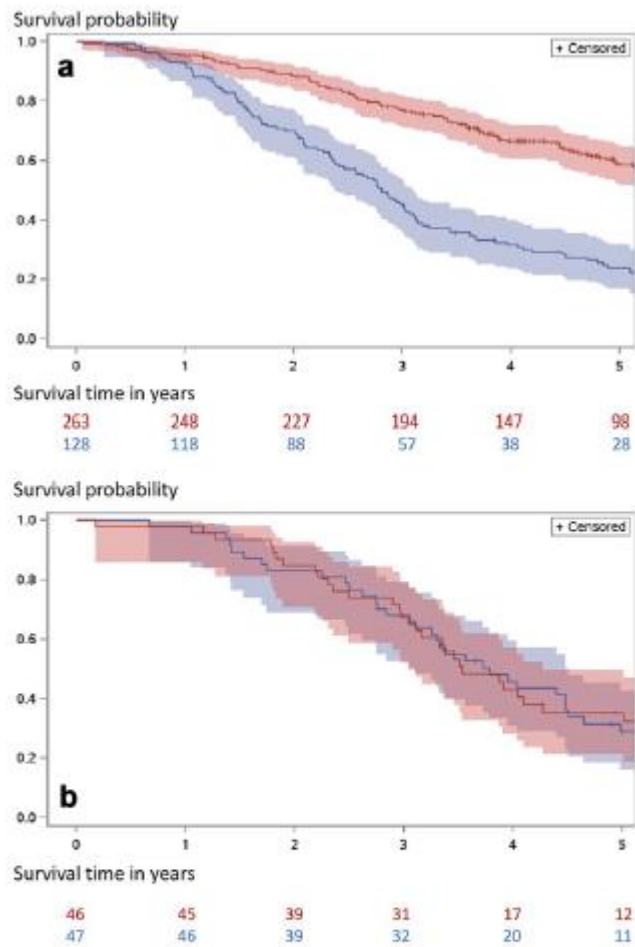
Local interventions for colorectal cancer metastases to liver and lung

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**Fig. 1 a** Five-year survival of 391 patients selected to have lung metastasectomy (red) or not (blue). **b** Ninety-three randomised patients were balanced for patient and cancer-related factor: age, sex, weight, lung function, primary colorectal cancer stage, interval since primary operation, carcinoembryonic antigen, liver involvement, number of metastases, performance status. The survival curves are superimposed

Dear Editor

The recent paper on “Local interventions for colorectal cancer metastases to liver and lung”(1) caught my attention. The authors kindly cited the preliminary report of the PulMiCC (pulmonary metastasectomy in colorectal cancer) randomised controlled trial (RCT)(2) of which I was a chief investigator. For non-specialist readers of a journal of medical science I should point out that Simsek and colleagues are in line with current international oncological belief and practice.

Their paper gives a clearly described analysis of 122 patients who had local interventions for lung or liver metastases ± systemic anticancer treatment during a 93 month period up to August 2021. Two groups were retrospectively defined by whether or not, at first follow up, they were radiologically free from residual disease (N=88) or not (N=34). Overall and progression-free survival (PFS) differed, with impressive tests of significance, P=.004 and P=.000 respectively.(1)

The full PulMiCC study recruited 512 patients into a prospective cohort who were to be offered randomisation to a control arm or to lung metastasectomy.(3) The belief in its survival benefit was so firmly entrenched(4) that the majority (263) had elective lung metastasectomy.(3) Figure The oncological and patient factors were balance in 93 randomised patients and median survival was actually a little longer in the control group (3.8 versus 3.5 years)(5). This was too few to prove “non-inferiority” but the results shattered the illusion that there would be near zero survival without metastasectomy(6) and claims that 40-60% five-year survival was attributable to the operation.

Lung metastases considered for resection are asymptomatic and are rarely if ever the cause of death — but they are the most easily imaged component of disseminated colorectal cancer. One could make a case for leaving them to facilitate monitoring of the response to systemic treatments but, as nails are to the apocryphal man with a hammer, they seem to be an irresistible target for local therapies.

Awareness that it may be the selection of those more likely to do well for the doctor’s preferred treatment creates an impression of benefit goes back a long way, well before RCTs were first done. In a letter to BMJ in 1899 about treatment of his own tuberculosis the sage physician Dr Daniel Samways wrote:

“Neither Switzerland, the Riviera, Egypt, the sea, or an English verandah, can justly claim patent right for the treatment of phthisis. Any of them may be statistically shown to be the best if the cases they treat are selected with sufficient care, and especially if their failures are quietly sent elsewhere.”(7)

When it was discovered, streptomycin was evaluated in a controlled trial.(8)

When there are many known and unknown factors determining length of survival with disseminated cancer, an RCT is more likely to get to the truth of treatment effects. Simsek and colleagues have written with suitable caution and state the limitations of their study in their conclusion but the absence of control data means that the impression of benefit is probably due to the well-informed selection of those naturally most likely to survive.

#### Legend to Figure

Upper panel shows five-year survival of 391 patients selected to have lung metastasectomy (red) or not (blue). In the lower panel 93 randomised patients were balanced for patient and cancer related factor: age, sex, weight, lung function, primary colorectal cancer stage, interval since primary operation, carcinoembryonic antigen, liver involvement, number of metastases, performance status. The survival curves are superimposed.

## References

1. Simsek M, Besiroglu M, Akcakaya A, Topcu A, Yasin AI, Isleyen ZS, et al. Local interventions for colorectal cancer metastases to liver and lung. *Ir J Med Sci.* 2023.
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.
3. 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.
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. 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.
6. Macbeth F, Fallowfield L. The myth of pulmonary metastasectomy. *Br J Cancer.* 2020;123(4):499-500.
7. Samways DW. Ocean voyages in pulmonary phthisis. *BMJ.* 1899;ii(30th December 1899):1817.
8. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis: a report of the streptomycin in tuberculosis trials committee. *BMJ.* 1948;ii:769-82.