

The Prospective Observational Cohort and the Nested Randomized Controlled Trial in the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC Study) Question the Reliance on Existing Evidence for the Magnitude of Benefit From Lung Metastasectomy

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Dear Editor

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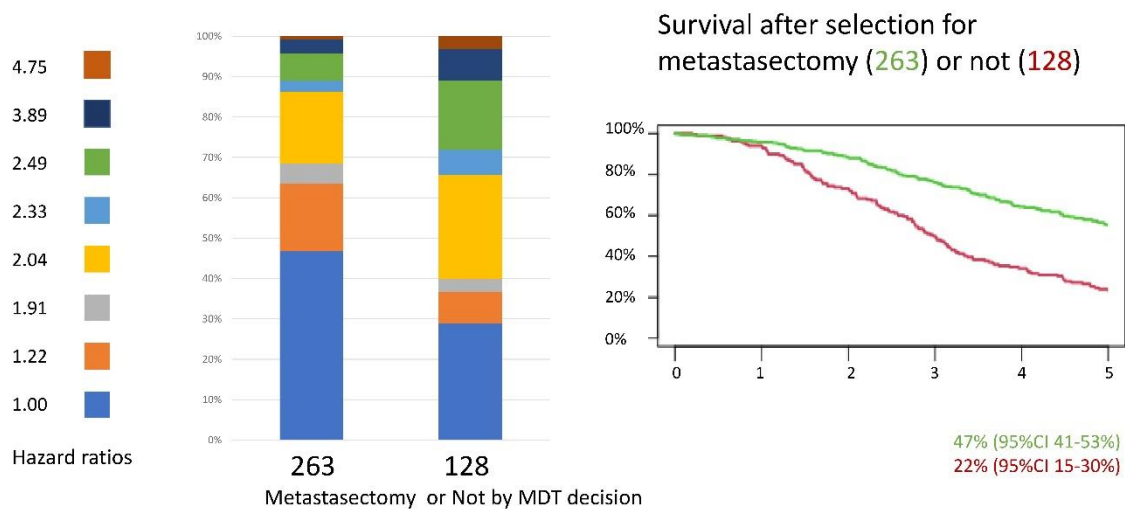
The excellent study by Alabraba and Gomez caught our attention.(1) In a systematic review performed to a high standard they draw attention to the burden of treatments in elderly patients with metastatic colorectal cancer (CRC). They conclude that the “survival benefit of treating CRC metastases with surgery or chemotherapy decreases with advancing age and QoL may decline in the elderly” and they go further to suggest that under certain circumstances which they specify, clinicians “may consider surveillance cessation in patients aged 75 years and above.” We fully support the second suggestion and the preparedness of the Nottingham group to challenge orthodoxy. We refer to further evidence as readers consider how these finding might influence their own practice.

On the question of the clinical effectiveness of surveillance, there have been 16 randomised controlled trials (RCTs) testing the plausible hypothesis that the earlier asymptomatic disease is detected, the more likely it will be amenable to surgical resection, and the better will be survival. The first trial of surveillance following resection of colorectal cancer tested effectiveness of the then novel use of the tumour marker carcinoma embryonic antigen (CEA). It recruited 1447 patients from 1982-1993.(2) As other means became available, surveillance became more intensive. The trials have been systematically reviewed and put through meta-analysis with the consistent finding that although more patients are found with operable metastases, surgery confers no survival benefit.(3, 4) It has been suggested that the impression of benefit is due to lead time bias and that the association between more metastasectomy operations and improving survival is reverse causation. Better survival due to implementation of treatments, proven in RCTs, provides more opportunities for metastasectomy.(5)

The Nottingham study(1) creates an impression of a high-quality evidence base but like nearly all analyses of metastasectomy, it lacks control data. In their Table 2 related to lung metastasectomy, there are only retrospective studies. In the text (but not the table) they kindly refer to our study Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) which had a prospective cohort of 512 patients of whom 481 proved to have CRC lung metastases. Their median age was 68 (IQR 61-74).(6) Of them 263 had elective (non-randomised) metastasectomy and for 128 it was decided to not operate. The median ages were 67 and 72 respectively ($P < 0.00001$, Mann-Whitney U test). The operated patients also had more favourable ECOG scores, lung function, CEA, liver status and more than twice as many had a solitary metastasis (65% vs 31%). These differences in age, function and oncological status would be sufficient to explain the survival difference of 47% and 22% in the observational cohort, but it required an RCT to better define the residual difference attributable to surgery.

The nested PulMiCC RCT (N=93) was rigorously conducted and analysed and is the most trustworthy means of excluding the many sources of bias in uncontrolled data.(7) The arms of the trial were well balanced for all known confounding factors and there was no difference in

survival at any time point (Figure). It is true that randomisation was compromised by the current orthodoxy found in authoritative published sources. An Editorial in the journal of the European thoracic surgical societies suggests an indicative figure of five-year survival with lung metastasectomy of 60%.(8) An American counterpart suggests that observational results can be compared with an assumed nil survival.(9) The 60% difference implied is incompatible with the evidence available, but such publications made the pre-trial acceptance of equipoise difficult to adhere to and undoubtedly played a role in inhibiting recruitment to the randomised trial. There were also detrimental effects on quality of life(10) and a similar decline in health utility in the two arms of the PulMiCC RCT.(11) Directly relevant to clinical oncologists is that the perceived survival benefit from surgical metastasectomy can be gained at lower risk with stereotactic radiotherapy. Radiation oncologists have been misled by the widespread entrenched belief in the clinical effectiveness of surgical metastasectomy but some are willing to share our own heretical thoughts.(12) Although it has been proclaimed that “Surgery for pulmonary metastases is a pillar of modern thoracic Surgery”(8) it is a pillar which has weak foundations.



Legend to figure

Kaplan–Meier survival curves. Overall estimated survival at 4 years was 47.1% (95%CI: 31.9%–62.6%) for control patients and 22% (95% CI: 15.3%–30%) for metastasectomy patients, with the respective 5-year survival values being 29.6% (95% CI:15.3%–45.7%) and 36.4% (95% CI: 21.3%–53.0%).

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