Lung metastasectomy for colorectal cancer: the impression of benefit from uncontrolled studies was not supported in a randomized controlled trial.

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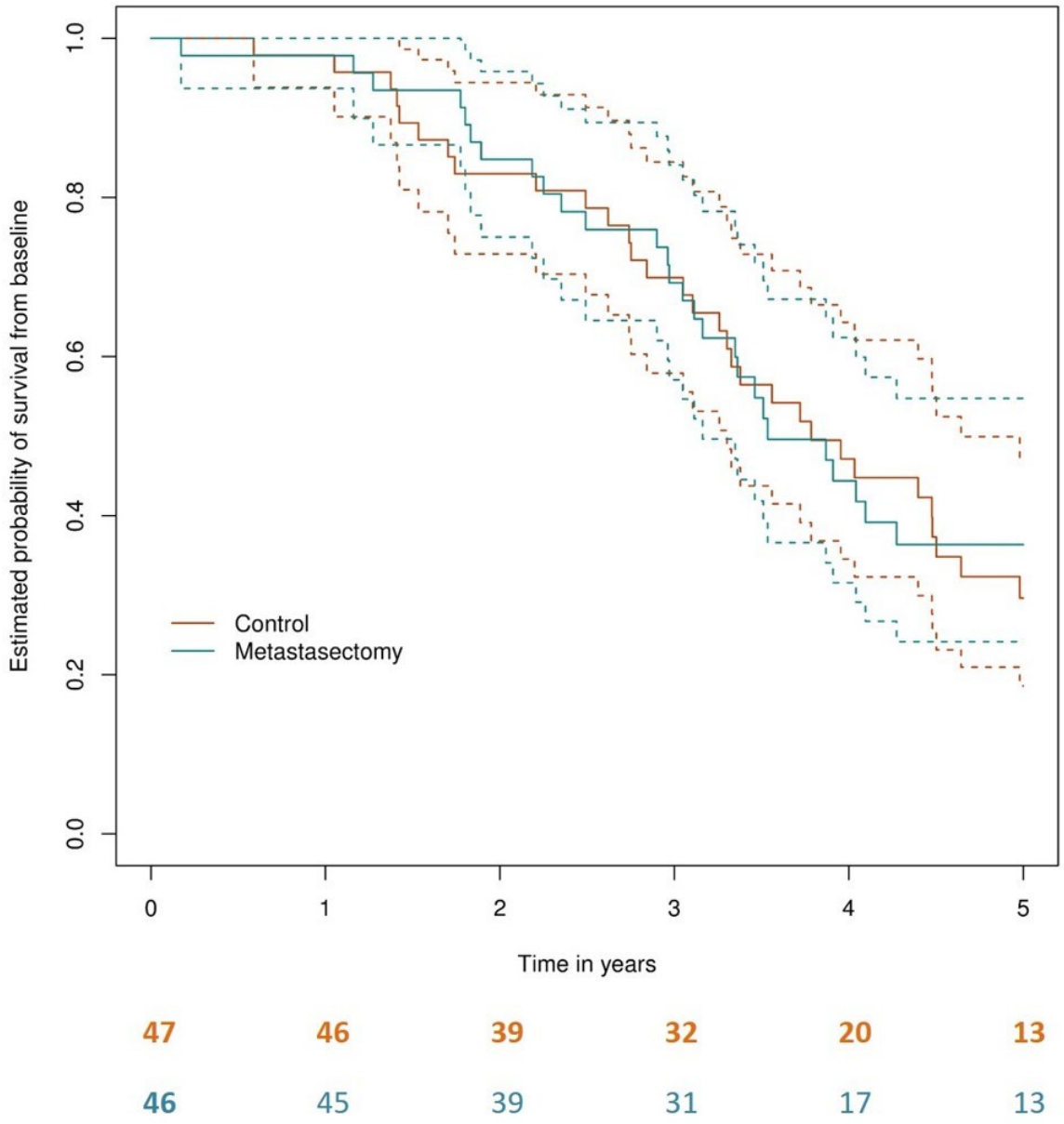
Central Figure. Abbreviated legend: The PulMiCC trial found no difference between lung metastasectomy and control.



The Society of Thoracic Surgeons (STS) Expert Consensus Document on Pulmonary Metastasectomy states:

> *'Since 1980, greater than 1,000 publications addressed PM, without a single randomized controlled trial. Most of the studies are surgical series, usually from a single institution, and include single or multiple pathologies. The pool of patients from which metastasectomy patients derive is not reported, allowing no comparative survival analysis. Historical controls are used or metastatic disease survival is assumed to be zero, a contention not supported by the literature.'*(1)

The STS statement nevertheless confirms the widely held assumption of zero survival, as the basis of a practice, unsupported by adequate evidence. No randomized controlled trial (RCT) was found. We have recently published the RCT Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) which puts something into that void.(2) [Figure 1/Central Figure]

A search in the late 2000s, for evidence about CRC lung metastasectomy, returned 101 publications reporting practice from the 1960s.(3) Most offered no estimate of what survival might have been without surgery. Only one paper attempted to address the question. Forty years ago, under the title *'The effect of metastasectomy: fact or fiction?'* Torkel Åberg and colleagues wrote *'It has been assumed, implied, or claimed that the 5-year survival without operation is nil. Control material is, however, lacking.'*(4) They had survival results for 70 patients who had lung metastasectomy between 1961 and 1978. [Fig.2] They had searched the hospital records of the era preceding adoption of metastasectomy in their hospital, seeking patients in earlier years, who would have satisfied their current criteria. They found 12. Three had lived for more than five years. It is a small number, and the 95% confidence limits around a 25% survival rate are wide at 5.5% to 57%, but it makes zero five-year survival improbable. Åberg's paper has metastasectomy in the title, and was published in Annals of Thoracic Surgery, but in a citation network analysis it was only cited twice among the 101 papers reviewed.(5) Thereafter, uncited, the paper dropped out of sight.

Of the 101 papers, 51 contained data suitable for analysis on 3504 patients.(3) None included control data, or estimates of survival without metastasectomy. Solitary metastases were removed in 60%, more than 60% had no CEA elevation, and the interval since the primary CRC resection shortened from about three years to two years during about 40 years of clinical experience. To derive an estimate of what the survival without metastasectomy might be, the Clinical Operational Research Unit worked with the Thames Cancer Registry to perform a mathematical modelling exercise.(6) Patients in the Registry whose age, sex, cancer stage and death free survival were similar to those in large clinical series, had a survival rate much higher than had been assumed.

The models informed the cautious power calculation of the PulMiCC trial (Pulmonary Metastasectomy in Colorectal Cancer) which was designed to show non-inferiority of non-metastasectomy.

PulMiCC opened in 14 centers and from December 2010 to November 2016 randomized 93 patients with CRC lung metastases, fewer than were hoped for. Of 512 patients who gave informed written consent to enter the study for evaluation, 82% were not eventually randomized. At the behest of the Data Monitoring and Ethics Committee the reasons for failure to randomize eligible patients in the three largest recruiting centers was investigated. Among 155 patients there were 41 patients who elected to make their own decision, 19—nearly half—chose not to have metastasectomy. For 78 patients the multidisciplinary team made the decision and 77 (99%) were operated on.(7) The patients showed equipoise, whereas the clinicians did not, probably because of the widespread conviction that without lung metastasectomy none of these patients would survive.(1) There was also pressure on them from clinical colleagues to fall in line with accepted practice in the management of metastatic colorectal cancer.(8)

In PulMiCC the known confounding factors were balanced by including a minimization step in randomization. The characteristics of the patients were in line with published papers [Table] except for the proportion of solitary metastases which was 37% (34/93) in PulMiCC, compared with 63% in a meta-analysis including nearly 3,000 patients.(9) This reflects reluctance on the part of multidisciplinary teams to randomize patients with a solitary metastasis. Multiple versus solitary metastases is associated with lower survival (hazard ratio: 2.04)(9) The overall five-year survival of patients assigned to metastasectomy was 36%(95%CI:15%-46%) in PulMiCC compared with 42% in the meta-analysis,(9) consistent with fewer solitary metastases being randomized. Among PulMiCC patients, five-year survival of patients with a solitary metastasis was similar at 6/16 in the control arm and 5/18 in the metastasectomy arm.(2)

Importantly, no control patients crossed over to have metastasectomy, or any form of ablation, as the initial treatment for their lung metastases. Subsequent treatments, including chemotherapy and radiotherapy, were few and similar in the two arms.(2)

In PulMiCC the median survival was 3.5 years in the metastasectomy arm compared with 3.8 years for control patients. It is worth noting that a 3-4 months difference might be regarded as worthwhile in much larger trials of chemotherapy but it was not significant, but signaling in favor of control. Scrutiny of the survival curves shows two lines weaving in and out of each other. [Fig.1] At four years the overall estimated survival was 47% (95%CI: 32%–63%) for control patients and 44% (95%CI: 29%–61%) for metastasectomy patients. Overall, the hazard ratio was 0.93 (95%CI:0.56–1.56). The results cannot exclude the possibility of occasional long-term survival, where metastasectomy appears to have removed the only residual disease. That would allow for the anecdotal cases which colleagues recall, but they are few, and not well documented.

Other than the small expected fall in tests of lung function in the first three months, there were no differences in Quality of Life.(7) The Health Utility instrument EQ-5D-3L (EuroQol

5 dimensions, 3 levels) showed similar losses in self-reported health status over the first two years after randomization.(10) [Fig.3]

At N=93 PulMiCC is large enough to draw some important conclusions about the true effect on survival. If the zero assumption were correct, the results should have been 0/47 control survival versus 17/46 (37%) among randomly assigned patients (P <0.0001,Fisher's test). However, the published estimate in the report of the meta-analysis it was moderated to 'worse than 5%', without credible evidence.(9) Running Fisher's test around the 5% estimate, for 2/47 (4%) and 3/47 (6%), Fisher's test gives P for difference <0.0001 and P<0.0003 respectively. If such results had emerged from PulMiCC, it is unlikely the trial would have been rejected because of small numbers, irrespective of any prior power calculation. The repeated dismissal of PulMiCC as 'too small' is surely because it was out of kilter with prior consensus.(1) Power calculations are done in order to reconsider trial designs with no realistic prospect of answering the research question but once the trial is done, and the data are in, the power calculation becomes irrelevant in the actual data analysis.(11) PulMiCC data are the most reliable available and in any future trial, the power calculation would have to take them into account in deciding the effect size to be used in determination of the sample size.

It is clear from PulMiCC that the control survival is much higher than has been widely believed. The same has been seen in the only other two RCTs testing local treatment of metastases, with radiofrequency ablation and with stereotactic radiotherapy and reporting overall survival.(12, 13) The authors of the RCT of liver metastasectomy wrote *'The study shows that local tumor ablation by RFA in combination with systemic therapy results in an excellent survival, which however was also achieved in the control arm.'*(14) Their interpretation lacks objectivity and their findings were at odds with the assumed near-zero survival assumption. The control patients in that trial, and in PulMiCC, provide a pooled total of 106 patients, eligible for local treatment of CRC metastases in the liver or lung. There was 30% five-year survival; the 95% confidence interval, derived using a complementary log–log scale, is 21% to 40%.

The question which arises is whether the better than anticipated control results is due to improving overall survival with the newer treatments. A systematic review in JAMA 2015 concluded "Gains from first-line therapies have been modest but consistent; however, gains from second-line therapies have been disappointing."(15) The meta-analysts pointed out the effect of lead-time bias: if diagnosis of recurrence is made sooner, it adds to time alive, creating a false impression of improved care. That, said multiple RCTs have shown that more intensive monitoring does lead to earlier diagnosis but this had not led to beneficial survival effect.(16, 17) The advantage of an RCT is that any of these gains, true or illusory, apply to both arms. Furthermore, the JAMA authors flag the possibility that increasing numbers of metastasectomies may be due to the increased opportunities presented by longer survival,

rather than the operations being the cause of longer survival. Critically to this discussion, they emphasize that "the most important conclusion to be drawn from this analysis is the indisputable value of enrolling patients in clinical trials."(15)

The apparently universal acceptance of near-zero survival raises more general points about cognitive bias and how opinions can override facts.(18) With constant repetition, falsehoods maybe perceived as the truth.(19) Human beings draw inferences from consistency with 'knowledge' and may be resistant to updating beliefs when facts change. At the first public presentation of the survival graph of PulMiCC at the conference *'Preventing Overdiagnosis and Over Treatment'* in Sydney, Australia, a thoracic surgeon rose and forthrightly declared that this RCT would convince nobody and that the control findings were erroneous because 'Big Data' shows 'nobody survives with unresected lung metastases'. Our colleague may be correct on the first point—the psychological research cited above supports his comment that evidence may not convince people to change their opinions(20)—but on the second point, there is an important misconception. Big databases include all patients with metastatic disease, rather than the 2%-3% selected for metastasectomy.(21, 22) Furthermore, Big Data misses prognostic factors—most of the known and all the unknown—so however 'big' the collection of data, conclusions are less reliable than a careful RCT. Databases of cancer treatments record therapeutic events. They cannot provide equivalent data on identical patients who, for whatever reason, did not have the treatment. Nor do surgeons have ready access to the outcomes of patients whom they have never met. Åberg had to search for his 12 comparator patients. Clinicians 'at the sharp end' may overestimate how large a proportion of a patient's survival is due to their efforts, and how much due to the selection of naturally longer surviving patients. Uncontrolled observational studies of other ablative modalities are being added to the literature at an alarming rate, in the belief that they can replicate the 'proven' benefits of surgery, with less invasive methods.

Our paper dwells on lung metastases from colorectal cancer. This is because it is the largest component of lung metastasectomy practice and therefore the most amenable to clinical trial and database research. It is likely that much of what has been learned in the last 15 years applies to other carcinomas. Sarcoma has a predilection to metastasise to the lung, and affects young people.(23) More often than not, further metastases become evident and the policy that has evolved is that in patients where the cancer runs an indolent course, reoperations are performed, selectively, until the loss of pulmonary function calls a halt. There are no

controlled studies to prove that it is surgery, rather than selection for surgery, that leads to an apparent association between lung metastasectomy and survival. Germ cell tumours are treated systemically and for them, lung metastasectomy may have a place in removing a necrotic lung mass and gleaning information about tumour response.

In medicine there must be retreats as well as advances.(24) Remember that radical mastectomy was the standard treatment for breast cancer for 90 years, until a trial of quite modest size displaced it. We need reliable RCTs to guide management of patients, not biased observational studies and 'belief'.

What should be the next step? We believe that these findings should ideally be confirmed (or refuted) in a larger RCT of local treatment of metastases (surgical or RFA or SABR) compared with no intervention, powered to show a clinically relevant improvement in 5-year survival. If this did confirm that there is a benefit, and the design included stratification with minimisation, it might also indicate for which patients it is most effective. Such a trial may be difficult because of the prevailing belief in effectiveness despite the lack of evidence but it is now essential to avoid possible wasted resources and avoidable harm to patients. Current and planned trials comparing different local treatments, and trials adding systemic therapy to one arm of a trial in which both arms have metastasectomy(25), cannot answer the question. Trials which have progression-free survival as the primary outcome are potentially misleading. Overall survival and Health Utility are the relevant outcomes. The cold light of reliable evidence still needs to be shone on this very uncertain area of oncological practice.

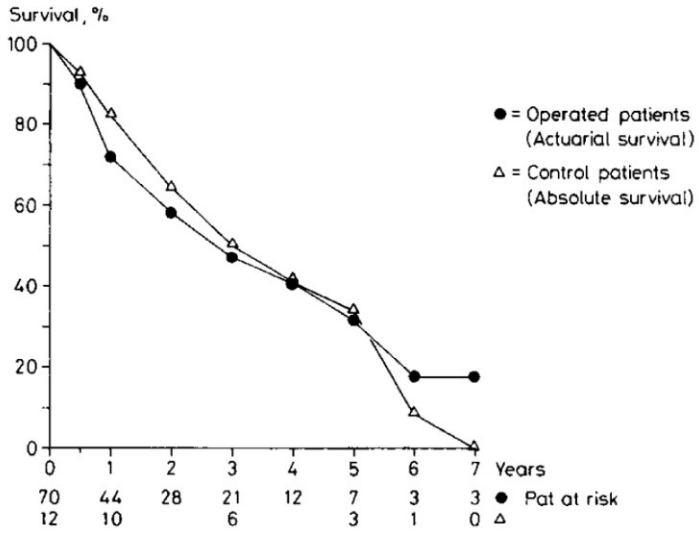


Fig 2. Survival after metastasectomy or diagnosis in 70 operated and 12 control patients.

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221 Figure 2

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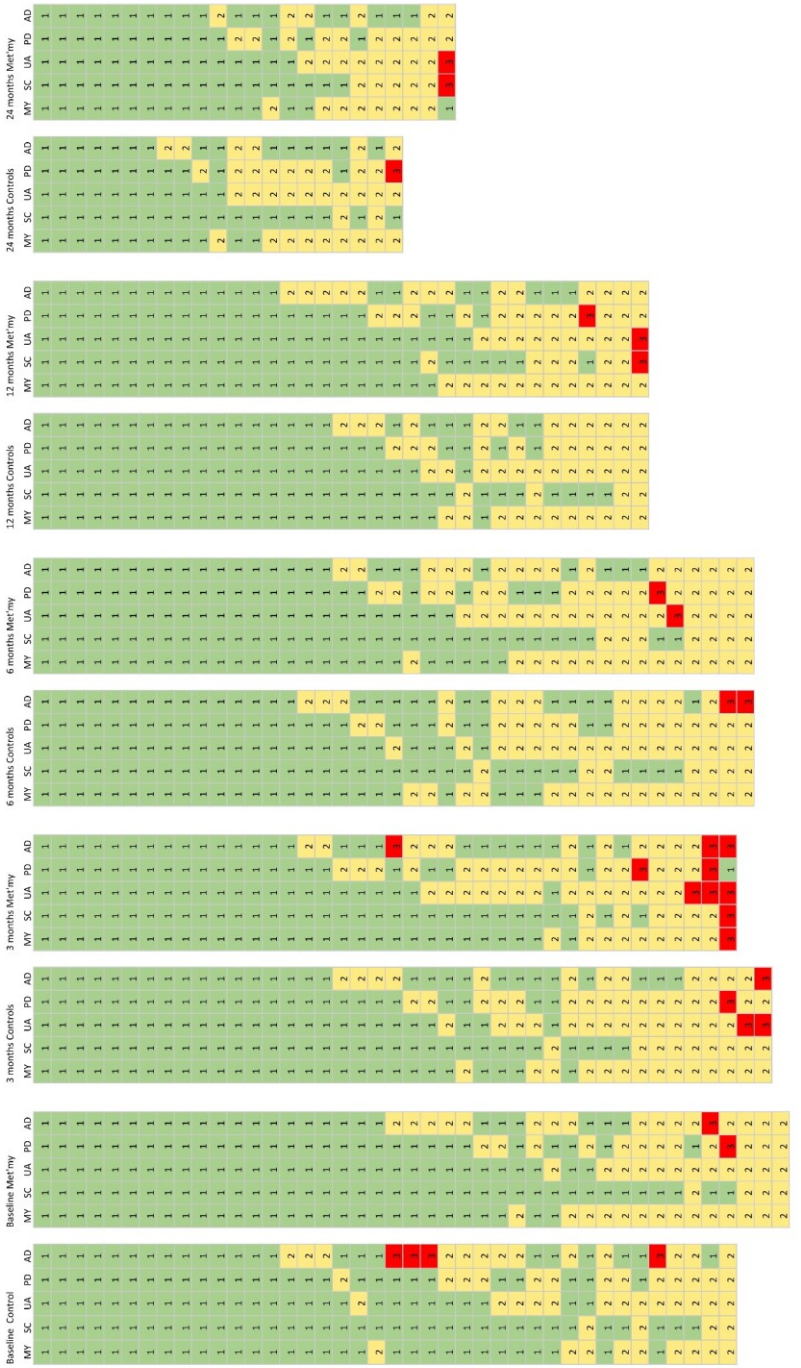

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224 Figure 3

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Legends

Central Figure. Abbreviated legend: The PulMiCC trial found no difference between lung metastasectomy and control.

Figure 1 The Kaplan Meier survival curves of the randomized controlled trial Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) in 93 patients. Overall Hazard Ratio 0.93 (95%CI:0.56–1.56).

Figure 2. A comparative study in 1980.(4) It explicitly contradicted the assumed zero survival.

Figure 3. 3-Level 3,2,1 scores in traffic light convention, in the 5-Dimensions of EuroQol (EQ-5D-3L) at baseline, 3, 6, 12 and 24 months, in the control (Left) and metastasectomy arms. Each horizontal set of five represents an individual's self-report of Mobility, Self-care, Usual activity, Pain/Discomfort, Anxiety/Depression sorted vertically in order of diminishing health state.

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