

Pulmonary Metastasectomy in Colorectal Cancer (PulMICC): Has the randomised controlled trial brought enough reliable evidence to convince believers in metastasectomy to reconsider their oncological practice?

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Introduction

In February 2019 the US Society of Thoracic Surgeons (STS) published their Expert Consensus Document on Pulmonary Metastasectomy which states that there has never been a randomised trial on the subject but that “metastatic disease survival is assumed to be zero”. This would mean that all survival beyond five years is attributable to metastasectomy[1]. The randomised controlled trial (RCT) Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) was published in May 2020[2]. PulMiCC contradicted those two statements: there was now an RCT and the control survival was not zero. Dirk Van Raemdonck (DVR) and Tom Treasure (TT) have worked within the European Societies since their inception and, in this context, on the ESTS Lung Metastasectomy Project[3]. Together we approached EJCTS offering to reflect on what had and had not changed in the intervening 10 years. We respect each other but do not share a consensus view- so in writing this article we keep our separate voices and are joined by our oncologist colleagues EVC and FM.

1.The ESTS Lung metastasectomy Project

Dirk Van Raemdonck (DVR)

Pulmonary metastasectomy (PM) is common oncological practice amongst thoracic surgeons. According to the latest annual database report by the European Society of Thoracic Surgeons (ESTS), resection of secondary neoplasms in the lung comprises about 12% of all pulmonary resections[4]. More than 10 years have now passed since the survey on PM practice by ESTS members was published by Internullo et al[5]. The results of this survey revealed a wide variability in surgical practice concerning the number of resectable lung metastases, the best surgical approach, the extent of resection needed, the best surgical device, the sequence for resecting bilateral lung metastases, and the role of repeated PM. The survey also confirmed areas of consistency: PM is not warranted in cases in which the primary tumour is not controlled or in which complete R0 resection of all macroscopic lung metastases is unlikely. The wide variability in surgical practice reflected the lack of clear guidelines based on solid scientific evidence. Therefore, in 2006, the ESTS brought together an international group of surgeons with the initial intention to evaluate the evidence and to generate guidance. It rapidly became clear that despite the great experience in performing this surgery, the belief in its benefit relied on uncontrolled observational case series and registry reports only. The ESTS working group concluded that the level of evidence for their routine practice was low and that robust guidance could not be produced[3]. A decade later the STS expressed similar caution and for the same reasons[1].

Tom Treasure (TT)

Editing the JTO Supplement, I worked with the authors to ensure that we incorporated all the available evidence and opinions. An opening speaker showed a picture of a recreational parachutist descending, proposing that the benefit of removing a metastasis was self-evident. It is true that there are many things done in surgery where we need no more proof beyond the immediate experience—relief of tension pneumothorax is an example—but PM, unlike a parachute, or relief of tension pneumothorax, is not done to avert imminent death. Most

patients in reported series of colorectal cancer go on to die of disease elsewhere. Given the degree of selection, might we be identifying longer survivors rather than influencing their survival? Metastasectomy demanded a more considered analysis.

The evidence base was follow-up studies of PM mainly from single institutions, systematically aggregated. Confining the analysis to a single pathology, colorectal cancer (CRC), and one site of metastasis (lung), it was possible to determine statistically valid statements about features associated with longer survival[6]. CRC provides the largest number of patients having PM so that was the disease we chose to study.

2.How the ESTS project influenced our work and thinking in the intervening 10 years DVR

Although Internullo's survey merely provided a time-sensitive perspective of the patterns of practice in PM, it is still the largest comprehensive examination of clinical practice in this field of thoracic surgery to date.[5] As no new survey has been conducted we can only speculate that the practice in 2020 has not much changed as no new evidence on the benefits or drawbacks of PM has been published in recent years.

TT

I returned to University College London to work on finding the best available information about CRC PM. We found 101 studies, 51 with data on 3504 patients. The characteristics of the patients were, in round figures, 60% men, average age 60 years, nearly 60% had primary rectal cancer, 60% were solitary metastasis, and 60% did not have elevation of carcinoembryonic antigen. The interval since primary resection was about 30 months. About 40% survived five years[7].

The sample size calculation for a trial is intended to avoid wasted effort in attempting to ask a question with too few patients. If instead of the improbable "zero"[1] we use the more commonly used estimate of <5%[6] the believed effect size is 35% gain in survival (~40% minus <5%). Here is a simplified illustrative sample size calculation for five-year survival for power of 80% and 90% at the customary 5% significance level.

Power	Alpha	Effect size	N
90	0.05	0.35	56
80	0.05	0.35	42

So a significant *difference* would have been shown with 93 randomised patients. A published mathematical model[8] predicted that survival in a matched population of cancer registry patients was very similar to the 40% reported, so we were testing *non-inferiority* of not doing PM, which required 300 patients. We used overall survival as the primary outcome, because metastasectomy removes the only disease on which progress can be monitored and progression-free survival is biased towards metastasectomy. From December 2010 to November 2016, 512 patients consented to enter the study. Only 93 were randomised. We

found that amongst a sample of 78 patients in the non-randomised cohort, 77 (99%) had PM when the multidisciplinary team (MDT) overrode randomisation. Amongst 41 patients making their own decisions, nearly half (19/41) chose not to have metastasectomy. The patients demonstrated equipoise; the MDTs failed to.

3. Personal experiences that have influenced our thinking and attitudes.

DVR

The million-dollar questions that remain are: 1) Is PM associated with cure? 2) Is PM associated with prolonged survival without cure? In other words, in patients with a systemic spread of their oncologic disease, can we expect an added value of a local treatment modality such as PM compared to systemic treatment alone?

According to a Surveillance, Epidemiology, and End Results database study, 5.6% of patients with rectal carcinoma and 3.7% with colon cancer had lung metastasis at the initial staging.[9] Twenty-five to 30% of CRC patients with no evidence of PM at diagnosis are prone to develop metachronous metastatic disease despite adjuvant systemic treatment, especially in those with known risk factors.

The PulMiCC trial struggled because only 18% of 512 recruited patients who gave informed consent to enter the trial, were randomised. Despite all efforts by the investigators to gain more evidence to answer the above-mentioned questions, the completed study is at risk of criticism. It remains to be seen whether the thoracic surgical community will be convinced of equal patient outcome without intervention and change its practice based on these trial results.

DVR and EVC are still believers in the benefit of PM in selected patients.

DVR/EVC

We would like to present the following clinical case:

Case vignette 1. A 45-year old female was diagnosed in 12/2008 with a rectal adenocarcinoma with bilateral synchronous pulmonary metastases, clinical staging UT3N1M1. Induction chemotherapy (5FU-Oxaliplatin) was given concomitant with radiotherapy (45Gy) to the pelvis. A rectal resection (TME) with lymphadenectomy and colo-anal anastomosis with protective loop ileostomy was performed in 04/2009. Pathology revealed a moderately differentiated intestinal type adenocarcinoma ypT3N0M1. She was given adjuvant chemotherapy (Folfox) until 11/2009. A pulmonary metastasis (1.2 cm) in the right lower lobe was wedged out in 02/2010. In 02/2011 a second metastasectomy was performed with segmental resection 1&2 in the right upper lobe for two nodules (4 mm & 6 mm) combined with a wedge excision of two nodules, one in left lower lobe (1.2 cm) and one in left upper lobe (0.9 cm). In 07/2012, two new metastases appeared in the left lower lobe. Chemotherapy with Folfiri/bevacizumab was started until 10/2012. A segmental resection 7&8 in left lower lobe for a peribronchial nodule (0.5 cm) was performed in 11/2012 followed by adjuvant chemotherapy with Folfiri/bevacizumab. Patient is currently alive and

active nearly 10 years following the initial diagnosis with no evidence of residual disease on PET/CT scan in 07/2020.

The question remains whether this patient would still have been alive without local treatment for her multiple and bilateral synchronous lung metastases.

TT

In the 1970s some patients had radical mastectomy and others had simple mastectomy. The difference in mutilation and lymphoedema was self-evident, but the likelihood of cure was a matter of conviction. In 1981 Umberto Veronesi published an RCT showing no advantage of radical mastectomy[10]. After 90 years Halsted's operation was replaced by surgery confined to treatment of the primary cancer. Many of own my patients, cardiac and thoracic, were recruited into controlled trials, testing treatment policies or technical details. In the adjacent operating room in the 1980s Peter Goldstraw was expanding the practice of PM. Why, I thought, was it not being tested for effectiveness?

Case vignette 2. In the mid-1990s a professor of physiology had a large central CRC metastasis, necessitating left pneumonectomy. I expressed my reservations, but I did not have the evidence to say no, and I was prevailed upon by our colleagues to operate. He died within the year of widespread disease.

Case vignette 3. In the 20-teens, a neighbour was visibly deteriorating. He'd had a colon cancer removed. Asymptomatic liver and lung metastases were resected. Recurrences were treated with further surgery or ablation. Following a liver operation, he had a pulmonary embolism, remained breathless, having daily heparin injections. Regional anaesthesia for a procedure damaged his spinal cord; he hobbled about with a stick. I visited him on his death bed. He trusted the doctors that these treatments were beneficial. I could see that unproven treatments had taken over the last three years of his life and marred its quality.

These men were not exceptions. The majority of people who have a lung metastasectomy die of colorectal cancer at other sites; lung metastases rarely cause death or symptoms.

4.Should recent published guidance from STS and NICE be reconsidered in the light of PulMiCC?

TT

There are now three RCTs which have found that among patients who met criteria for local treatment of metastases, but who were randomly assigned to not have it, survival was nearly 30%. Taken together the RCT of liver radiofrequency ablation and PulMiCC provide 106 control patients who had neither intervention. The combined survival was 29% (95%CI: 22%-37%)[11]. That is significantly different from <5% (P=0.001). So, there is Level 1 evidence that survival of patients who are at present candidates for PM is well above the 0-5% estimate which was never based on good data.[12]

A strong point of PulMiCC is the excellent balance between the trial arms. It reflects ‘real world’ clinical practice. But 47% of patients had a solitary metastasis, fewer than the usual ~60% due to the reluctance of teams to randomise these patients. PulMiCC found a median survival of 3.5 years after metastasectomy compared with 3.8 years in controls.[2] The Kaplan Meier analysis of PulMiCC showed no significant difference, but with wide confidence intervals due to the relatively few (N=93) randomised patients. [Figure.1] PulMiCC does not exclude the possibility of a much smaller benefit, but the large majority go on to die of their cancer. The lung metastasectomy was possibly an inconsequential event along the way.

DVR

The STS enlisted its Workforce of Evidence-Based Surgery to provide clinically relevant guidance to clinicians despite the limitations of the literature on PM [1]. The authors of the document concluded that “*Best practice for PM in cancer management remains uncertain. As with other areas of oncology care, physicians must hold themselves to evidence-based clinical standards as best as possible, and avoid the trap of doing something because it can be done. The art of medicine is alive and well in many aspects of oncology care. Ideally, continual review of current oncologic literature, familiarity with national and societal guidelines, multidisciplinary, and shared decision-making approach to patient care provides a framework for clinical care recommendations, even when a pure evidence-based approach is not possible.*” Until today the practice of PM widely continues.

According to the STS expert consensus document, 92% of the members of the task force strongly agree and 8% agree with the following statement: “*In CRC patients, PM can be considered within a multidisciplinary treatment construct, with systemic therapy before and after PM*”[1].

The summary of the NICE guidance on metastatic CRC in the lung states “1) *Metastasectomy, ablation, or stereotactic body radiation should be considered for people with lung metastases that are suitable for local treatment, after discussion by a multidisciplinary team that includes a thoracic surgeon and a specialist in non-surgical ablation;* 2) *a biopsy should be considered for people with a single lung lesion to exclude primary lung cancer*”[13].

DVR and EVC believe that this guidance should stand as the new published data of the PulMiCC trial are not strong enough to convince believers in local therapy to stop their current surgical practice. We believe that PM may occasionally cure patients that otherwise would have to continue to live on with metastatic disease. On the other hand, we believe that PM is part of the multimodality treatment that contributes to prolonged survival in patients with persistent or recurrent metastatic disease. In some way, PM can be considered as a form of local cancer control that could be called “surgical chemotherapy”. Contrary to TT we would have used progression-free survival as an outcome parameter in the PulMiCC trial to investigate whether local treatment of pulmonary metastases contributes to cancer-free survival in these patients.

5.A question for non-surgical colleagues: where should surgical metastasectomy now fit in oncological practice for advanced colorectal cancer?

Eric Van Cutsem (EVC)

There is nowadays a consensus based on data from large studies of liver metastases and from studies (often case series) of lung metastases of colorectal cancer that treatment strategies for patients with oligometastatic disease (OMD) should be based on the possibility of achieving complete ablation of all tumour masses, using surgical R0 resection (complete resection with clear resection margins and no evidence of microscopic residual tumour) and/or alternatively other local ablative therapies, either initially or possibly after induction treatment with systemic therapy, for both the primary tumour and metastases. For patients with OMD confined to a single organ (most frequently the liver), or a few organs (pre-dominantly visceral metastases, e.g. lung), a potentially curative approach exists[14]. And hence many efforts are going towards more optimal selection of patients in order to minimize the chance of recurrence. Indeed, in the optimal selection of patients for resection technical challenges, as well as oncological challenges do play an important role. There is also a growing consensus that in this situation chemotherapy (neo-adjuvant and adjuvant) as well as resection of resectable oligometastatic disease, contributes clearly to an improved outcome, which is expressed by an improved progression-free survival and overall survival.

Fergus Macbeth (FM)

The management of colorectal cancer has evolved hugely over the past 30 years with the use of adjuvant chemotherapy, pre-operative radiotherapy for locally advanced rectal cancer and laparoscopic surgery, and improvements in systemic chemotherapy and immunotherapy. All have been underpinned by evidence from randomised controlled trials. Meanwhile PM has been increasingly used and is now widely seen as a standard procedure without any randomised trial evidence to show that it improves overall survival. The only randomised trial, PulMiCC[2] in fact shows no difference in survival up to 5 years between patients who did and did not have metastasectomy.

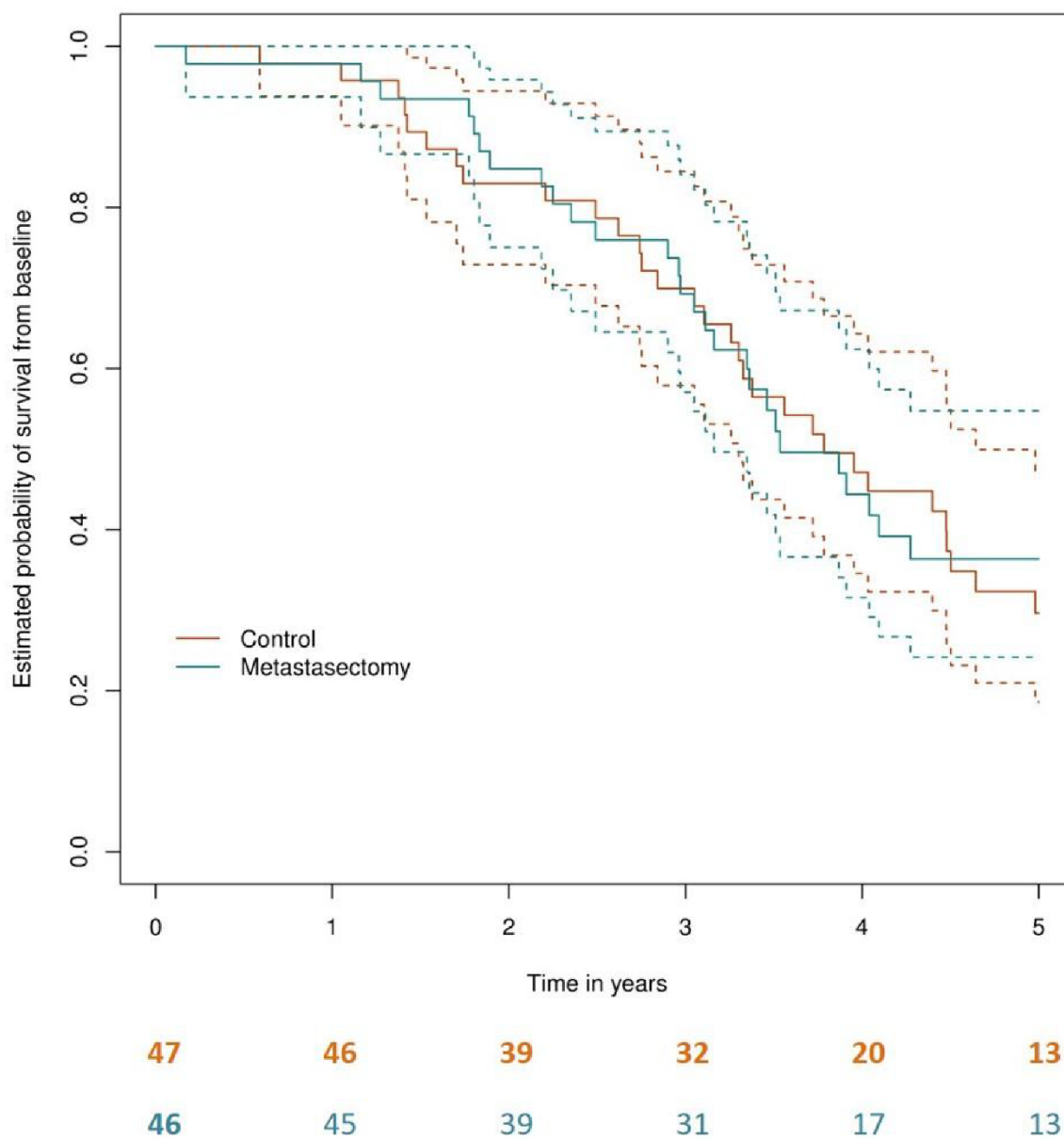
The many observational series cited as evidence for metastasectomy are flawed by selection bias and immortal time bias. An example is the study of Kim et al who reviewed the outcome of 105 patients (collected over 10 years) who developed lung metastases after radical treatment of colorectal cancer[15]. Of those, 57 had lung metastasectomy and 48 did not. There was a significant difference in survival probability of around 50% at five years, but also important differences in key prognostic factors. The operated patients were younger and 96% had fewer than three metastases compared to 33% in the unoperated group.

It is possible a few patients may benefit from lung metastasectomy but metastatic disease, once developed, is generally believed to be a systemic problem, unlikely to be cured by a local treatment. In the vignette introduced by DVR and EVC, the PM operations clearly failed in the primary intent to remove all residual disease in the first instance. She has had four episodes of RCT-proven chemotherapy which are likely to be the reason for her continued survival, while the PM operations merely improved the appearance of the chest x-

301 rays. The results of PulMiCC have clearly shown that without metastasectomy well-matched
302 control patients do not almost all die within 5 years as is so widely stated. The onus now is on
303 the believers in metastasectomy to show convincing evidence that it significantly improves
304 overall survival and quality of life, because PulMiCC indicates that it may not. No cancer
305 drug would get approved or into routine practice without such evidence, so why should
306 metastasectomy with its finite risks and costs?

308 **Conclusion**

309 The two sides disagree on whether policies of PM for CRC should be changed, based on the
310 PulMiCC trial. Where we can agree is that there is Level 1 evidence that the 0-5% survival
311 estimate is erroneously low and that the uncertainty about the clinical effectiveness of PM
312 makes it ethically justifiable to collaboratively design an RCT which might definitively
313 resolve this disagreement.



Legend to the figure

Kaplan–Meier survival curves for the control and metastasectomy arms (with 95% confidence intervals) in the Pulmonary Metastasectomy in Colorectal Cancer randomised controlled trial.

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