



# Pulmonary metastasectomy: limits to credibility

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**Abstract:** Lung metastases are a common site of spread for many malignant tumours. Pulmonary metastasectomy has been practiced for many years for sarcomas and is now becoming increasingly frequently advocated for patients with many other tumours, especially colorectal cancer. In this article we argue that this procedure is one framed by therapeutic opportunity and not supported by strong evidence. It is potentially harmful and may not be effective. Our argument is based on several important issues: (I) the vagueness of the concept of “oligometastases” and its biological implausibility; (II) the flaws in the often-cited observational evidence, especially selection bias; (III) the lack of any reliable randomised trial evidence of improved survival but evidence of harm; (IV) the failure of strategies to detect metastases earlier to influence overall survival. The introduction of stereotactic radiotherapy and image-guided thermal ablation have made the urge to treat lung metastases stronger but without any good evidence to justify their use. We acknowledge the problems of carrying out randomised trials when there is a clear lack of equipoise in the clinical teams involved but believe that there is an ethical need to do so. Many patients are probably being given false hope of cure or prolonged survival but are at risk of harm from pulmonary metastasectomy or ablation. It is possible that a few patients may benefit but without better evidence we do not know which, if any, do.

**Keywords:** Pulmonary metastasectomy; thoracic surgery; cancer; oligometastatic disease

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*“You believe that easily which you wish for earnestly.”* — Terence, from his play *Phormio* 161 BC.

## Introduction

Without any apology, we admit that the aim of this article is to question the role of pulmonary metastasectomy—a procedure which we believe is without logical foundation or reliable supporting evidence. We have no relevant financial or academic conflicts of interest as we are both long retired from clinical practice. But we are driven by a desire to see rationality brought to the topic and to ensure patients are spared pointless and perhaps harmful intervention. Our introductory material is based on a presentation at the

2019 World Lung Cancer conference in a “Controversy Session” (1). Speakers were invited to be provocative and we approach this article in the same spirit.

The Controversy Session was given the catchy title “Hunting a ghost for 25 years - Will We Ever Catch OMD?”. The abbreviation “OMD” indicates that “oligometastatic disease” is seen as an established diagnosis but all four speakers pointed to the lack of an agreed number or indeed whether OMD could be defined by a specific number (1-4). A clinical state characterised by “fewness” of metastases should alert everyone to the vagueness and uncertainty of such a diagnostic label: any threshold number for inclusion is likely to be arbitrary. Here we present a sceptical view of the diagnosis of OMD

and its treatment, based on a logical sequence of hypothesis, evidence and rebuttal (5). Rather than a ghost which we might catch, as suggested by the title of the International Association for the Study of Lung Cancer (IASLC) Controversy Session, we are inclined to regard this as an oligometastatic myth.

### A bit of biology

Lung is one of the commonest sites for metastasis. The cancer reaches the lung parenchyma in the mixed venous blood. Other than in situations where there is a right to left shunt, the lungs provide a filtering mechanism. The seed and soil concept promoted by the London surgeon, Stephen Paget (6) explains the predilection of some cancers for certain sites, but the basic mechanism of filtration by the lungs remains an important factor (7). Because modern computerised tomography (CT) scans have excellent resolution, lung metastases more than a few millimetres in diameter can now be detected in reasonably healthy lungs. The metastases also will also show up on fluorodeoxyglucose positron emission tomography (FDG/PET) scans.

It is a matter of common observation that a patient whose primary tumour has been removed and is apparently disease-free can subsequently develop metastases. These previously undetected micrometastases were always there but were below the limits of imaging sensitivity. So, it is sadly true that in patients with one or a few metastases, more almost always become evident over time. Why then is it logical to believe that patients with a few detected metastases might be rendered disease-free by removing them? It would be like standing under a tree in the autumn and seeing one fallen leaf and believing this to be a unique event. In nearly all cases, if you look up, you will see others on their way down. This is why it was accepted 25 years ago that the presence of even one metastasis should be seen as evidence of disseminated disease. It meant that metastatic disease required systemic rather local treatment if survival were to be influenced.

We can pinpoint the explicit acceptance of this understanding for both breast and lung cancer.

There had been a growing case during the 1970s for breast surgery to be conserved for management of the primary cancer (8-10). If the cancer had the propensity to metastasise it should be regarded as systemic from the outset

and managed with adjuvant systemic treatments. Halsted's radical mastectomy was then gradually abandoned, sparing millions of women mutilating but unavailing attempts at surgical "cure" (11,12). This change of approach was generally welcomed. However there is a report from 2006 of a surgeon removing as many as 124 lung metastases from breast cancer at one operation (13). He appeared confident that there was not a 125<sup>th</sup>—an instance of believing what you "*wish for earnestly*".

For lung cancer, better detection of lymphatic and blood borne metastases, spared many patients an unavailing thoracotomy. Fewer were operated on but 5-year survival rates for those who were improved from about 25% (14) to better than 50% (15) because of better detection of metastases at diagnosis. Promotion of extensive mediastinal lymphadenectomy has led to a return to operating on patients whose cancers have spread beyond primary resection, despite a lack of secure evidence (16). This is probably a backward step when there has been an evidence-based move away from radical clearance of lymph nodes in the surgery of breast, colorectal and ovarian cancers (8,10,17-20).

### Oligometastasis—a made up term

The promotion of treatment of blood borne metastases under the banner of OMD now threatens to put the clock back to a more reckless approach to cancer surgery. In 1995 Hellman and Weichselbaum wrote "*Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.*" (21). They then went on to hypothesise, without offering any evidence, that this might not always be the case. They proposed the term "oligometastases" to describe a clinical state between freedom from metastases and their "extensive and widespread" presence. They offered no plausible biological mechanism and none has been offered since. If the frequency distribution of the number of metastases showed a bimodal distribution with a second mode in the 1-5 or 1-3 range then there would be a mathematical reason to suspect there are two disease types, polymetastatic and oligometastatic. But there is no evidence that there is such a distribution. It is more likely that there is a skewed distribution with long tail tapering off to the uncommon state of a truly solitary metastasis.

**Box 1** Framing disease by its response to treatment

Diagnostic frames shift over time. In the 18<sup>th</sup> century the term “dropsy” described a condition which we would recognise as severe generalised water retention, or oedema. William Withering observed that some people with dropsy were helped by infusions of foxglove. Richard Bright discovered that some had protein in their urine and at autopsy he found shrivelled kidneys. So, the *clinical* diagnosis of dropsy was split and reframed by *morbid anatomy* according to whether it was the heart or the kidneys that failed

Clinical science over the next 200 years framed the many types of kidney disease but then treatment became possible with dialysis and transplantation. Long-term survival was possible but crippling expensive for most individuals and their families. In 1972 US Congress passed Public Law 92-603 and with it framed a new diagnosis: end-stage renal disease (ESRD). Patients with ESRD were entitled to federal funding. In 1974 ESRD appeared for the first time in PubMed in a paper about public financing. ESRD has been used in titles or abstracts 15,282 times since and runs at over a thousand citations a year

Another familiar example was the emergence of non-small cell lung cancer (NSCLC) as a diagnostic frame. In the 1970s, adenocarcinoma, squamous cell and large cell anaplastic cancer were framed by *microscopy*. Operation offered 25–30% 5-year survival, but for oat cell (or small cell) cancers, surgery nearly always failed due to widespread metastases. The new chemotherapy drugs made small-cell carcinoma melt away, if only temporarily. It may seem strange to frame a disease by *what it is not*, but that is exactly how NSCLC is framed. Lung cancer was dichotomised based on response to treatments. Interestingly NSCLC is now being unbundled by tumour markers, genomes and targeted treatments and reframed as a result

**Framing disease by therapeutic opportunity (Box 1)**

OMD is no more and no less than what is on the label—it describes cancer with few metastases. If there is no cogent biological mechanism, and there is an arbitrary cut-off in a continuous distribution, we are left to conclude that OMD is “framed” by the therapeutic opportunity it offers (1,22). Metastases fewer than can be counted on the fingers of one hand are amenable to local eradication with surgery, stereotactic ablative radiotherapy (SABR) or image-guided thermal ablation (IGTA). With more than five metastases it becomes increasingly impractical to attempt local control. The surgeon of the 124 lung metastases, resected an average of 10 in a total of more than 300 patients (13) but placing some limit on the number you can treat makes sense to most doctors. For SABR it has been said that there must be “few enough to zap”. So, it seems that this is the art of the possible rather than a precise science. The final speaker in the Controversy Session remarked that OMD was something “just made up” adding with characteristic Australian bluntness “by a couple of blokes in a pub!”. Five or fewer identified metastases fits a working definition of OMD (23). It is the therapeutic opportunity that makes OMD a useful working diagnosis and in an international survey 99% of 1,007 radiation oncologists regarded OMD as something for them to treat (24).

**Observational evidence of outcome...: case reports, surgical series and a registry**

From 1987 (about the time when metastasectomy came into

regular usage) to the end of 2018 there have been 2,166 papers with metastasectomy in the title or abstract. The rise has been exponential. Pulmonary metastasectomy for sarcoma became an established practice from the 1970s, rather than being an occasional individualised decision, as it had been up to then. Pulmonary metastasectomy became a standard of care (25). One underlying reason is that of patients with sarcoma who have metastatic disease, the lungs are affected in 80% and are the only site in 60% (26). Another is that these are often young patients, but why the young should suffer needlessly deserves some thought. There is still a need for proof of clinical effectiveness. Memorial Sloan-Kettering authors have revisited their original series after two decades (27,28) and they have found, along with others, that long survival with this disease is possible but in the absence of direct controls or even cogent comparison data (29) they have not proven that survival is a result of lung resection (30). Claims have been made that with repeat metastasectomy results are even better, neglecting the inescapable conclusion that this is because there is a dwindling denominator of people living long term with metastatic disease whose lives are punctuated by episodes of treatment to which their longevity is erroneously attributed (31).

The Memorial Sloan-Kettering surgeons reported their series of operations for the more common primary source, colorectal cancer, in the 1970s and published 10-year results in 1992 (32). In patients with metastatic colorectal cancer, it has consistently been found that the most powerful determinants of the length of survival is a solitary metastasis and

a long interval since primary resection (average 2–3 years) (33). But there was a growing mood that, provided the metastases were technically amenable to resection, their number was no obstacle and that neither early nor synchronous appearance of lung metastases was a barrier to operation. However, these patients with less constrained indications for metastasectomy were not doing well. The joint publication with Duke University in 2009, including 378 patients, concluded with a firm statement that “*Medical management alone should be considered standard for patients who have both three or more pulmonary metastases and less than 1 year DFI.*” (34). That advice has not been heeded.

### A fair test of clinical effectiveness: randomised controlled trials (RCTs)

The central problem is that there have been no attempts to quantify what would be the probability of survival for similar patients *not* having a metastasectomy. In 1980 Aberg challenged the practice pointing out that the survival times claimed as attributable to surgery might have been the result of selecting patients more likely to survive naturally (35). His paper has been overlooked and ignored, while authors more often cite those who agree with them (36). The publication of the International Registry of Lung Metastasis (37) reported on 5206 patients. It is regarded as the landmark publication, but it contains data only from patients who had metastasectomy with no attempt to offer a comparator.

The OMD hypothesis can only be reliably tested in RCTs. We are aware of only three RCTs of treatment of carcinoma metastases, comparing active local treatment with “no treatment”:

- (I) CLOCC is a trial of radiofrequency ablation of liver metastases from colorectal cancer (38);
- (II) SABR-COMET is a trial of stereotactic radiotherapy ablation of metastases from any primary carcinoma to any secondary site with the exception of specified patterns of brain metastases (39);
- (III) PulMiCC is a trial of surgical metastasectomy of lung metastases from colorectal cancer (40).

All three RCTs are small with 119, 99 and 65 participants randomised respectively.

Because the number of metastases is the most powerful prognostic factor it is very important that the frequency of metastases is well balanced in the two arms of the RCT.

The CLOCC trial reported no significant survival difference at 5 years (41) but a survival difference at 5–10 years, favouring ablation, with only 11 patients still

alive. But the ablation arm included more patients with solitary metastases (25% versus 12%), and fewer with 5+ (37% versus 56%) than the control arm. This important imbalance is likely to have influenced the outcome (38).

SABR-COMET randomised patients with five or fewer metastases and appeared to show a benefit favouring intervention (hazard ratio 0.57, 95% CI: 0.30–1.10;  $P=0.090$ ). But again, there was an important imbalance in the distribution of metastasis frequency. The stratification was set at between 1–3 and 4–5 metastases and, by chance, there was a 10% excess of solitary metastases in the intervention group (46% versus 36%).

There was also an important imbalance in the primary site. The 99 patients included those with more than five different primary sites and more than five different secondary sites and so it is not surprising that the two arms included patients with very different characteristics, some well-known to have prognostic significance. For example, the intervention arm had a predominance of patients with breast and prostate cancer likely to have a better prognosis. So, the seemingly impressive survival benefit in this small randomised Phase 2 trial is less meaningful in light of this prognostic factor imbalance and the upper limit of the 95% CI being 1.10. The SABR intervention arm also showed a 20% increase in Grade 2 or worse adverse events and a 4.5% rate of treatment-related deaths.

In the PulMiCC trial balance was ensured by including minimisation in the randomisation process (42). It demonstrated no significant difference in survival. The hazard ratio for death within 5 years, was 0.82 (95% CI: 0.43–1.56) (40).

Observational follow-up studies of lung metastasectomy (33) generally report 5-year survival of around 40%. Because it is assumed that the 5-year survival of a comparable untreated population would be near zero, this survival is always attributed to the effect of the operation. Of relevance in the three RCTs is the survival in the control arms. In both CLOCC and PulMiCC the 5-year survival of the untreated controls was around 30% and in SABR-COMET the 3-year survival was around 25%. In light of these findings, the belief that the absolute increase in survival approaches 40% at 5 years is no longer justified.

As far as we are aware there have only been these three RCTs addressing in various ways the value of removing or ablating oligometastases, all very small. Two (SABR-COMET and CLOCC) are potentially flawed by imbalances in key prognostic factors. PulMiCC shows no difference in survival. We acknowledge that the point

estimate of the hazard ratio in all three appears to favour intervention but believe that the question remains open. Despite all those with vested interests who might argue otherwise, larger definitive trials are ethically justified and still needed to determine whether this policy does in fact improve survival and, if so, in which patients. It remains very probable that many patients are being harmed without any real benefit.

### Why were so few patients randomised?

It is likely that thousands of patients around the world are undergoing metastasectomy every year but only 283 have ever been entered into RCTs. This could never happen with a new pharmaceutical intervention. In CLOCC there were 119 patients (control 59; intervention 60); in SABR-COMET 99 patients (control 33; intervention 66) and in PulMiCC 65 patients (control 33; intervention 32). Neither CLOCC nor SABR-COMET described the process of screening for recruitment and the size of the population from which the few randomised patients were drawn. In PulMiCC we have information (with informed consent) from all 512 patients considered in Stage 1 of the trial recruitment process. The three most actively recruiting centres were asked to provide reasons why patients in Stage 1 were not subsequently randomised. We wanted to establish who made the decision not to randomise and what clinical management then followed. If participants were deemed ineligible, we asked for the reason. Of 155 patient participants in Stage 1 of the trial, 41 decided not to be randomised and to make their own decision. Of these, 22 opted to have metastasectomy and 19 not to. When the clinicians made the decision 77/78 (99%) patients had metastasectomy. Ten patients had other pathology, nine lung cancer and one carcinoid. The protocol placed no constraint on the number of metastases but one unit set its own limits at 2–4 excluding patients with only one metastasis from the trial.

All this suggests that the clinicians did not really have equipoise about the value of metastasectomy whereas the patients did. With such widespread prior belief, it is no surprise that participation in RCTs is so rare.

### Trials of earlier detection of metastases for treatment

The first RCT testing the merits of post-primary resection monitoring with carcinoembryonic antigen screening was

the CEA Second Look (CEASL) trial which recruited from 1982 to 1993 (43,44). The interest was in treating early local recurrence but included the then growing practice of liver metastasectomy (45) and some lung metastasectomy operations. There was no survival advantage but instead a detrimental effect, but not to the level of statistical significance.

There have now been 16 RCTs including 3,325 patients and two meta-analyses investigating whether or not increased surveillance of radically treated patients with colorectal cancer improves survival (46,47). More intensive monitoring with increasingly sensitive tests appears to detect metastases about 1–2 years sooner. This results in more patients getting liver and lung metastasectomies, but there is no demonstrable survival benefit.

### Some conclusions from the limited evidence

Observational studies without reliable controls, very small RCTs with important imbalance in key prognostic factors, and the meta-analyses of monitoring trials leave us without strong evidence that the surgical removal or ablation of metastases improves survival. But why do so many clinicians believe that it does and persuade their patients to be treated? There are two reasons.

First, confirmation bias is a powerful force and the “evidence” from observational studies appears convincing to a believer. But although these suggest an association between treatment of metastases and longer survival time, we know that there is longer natural survival with fewer metastases. The association may not therefore be causation and it might be that a longer time alive provides opportunities to give more treatments. You can only treat the survivors. OMD is metastatic disease distinguished by an arbitrarily defined fewness of metastases. By selecting for treatment on the basis of fewness you are choosing the least aggressive cancer cases. If we attribute survival to treatment when it is in fact due to selection, we can delude ourselves. We may be engaging in “wishful thinking” (48).

Secondly, there is a lot of money already invested (24). There is also a lot of money to be made by industry, for-profit medical providers and by interventional practitioners. That is the reality. Surgical resection of lung metastases was already commonplace by the end of the twentieth century, certainly for sarcoma and increasingly for colorectal cancer (49). What probably has led to increasing interest in OMD as a treatable state has been the development of SABR and IGTA. This has meant that radiation oncologists and interventional

radiologists eager to use their new technologies could get in on the action. The inappropriately enthusiastic and uncritical commentary that accompanied the publication of SABR-COMET reflects that (50).

The vision of managing cancer in a similar way to other chronic diseases is seen as justification for metastasectomy. Cancer may run a chronic course during which the patient leads a good life, punctuated by treatment. But the survival advantage attributed to treatment may be greatly overestimated and the potential harms underplayed or under-reported. While there may be a correlation between the number of treatments and the length of survival, ongoing survival provides opportunity for more treatments to be given. We understand the need for clinicians to offer their patients apparently life-prolonging interventions, but we hope that they can look at the actual evidence more critically and seek trustworthy comparative data. Without those, their recommendations may be mere wishful thinking and their patients will be given false hope and hollow promises.

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