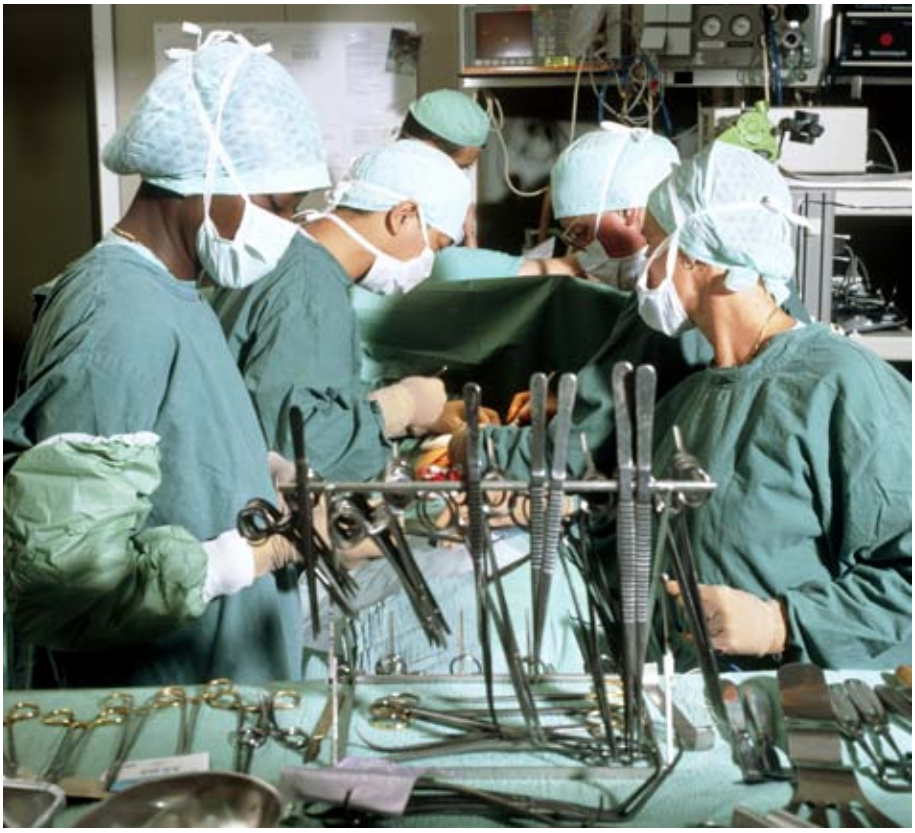
Surgical removal of asymptomatic pulmonary metastases: TIME FOR BETTER EVIDENCE

Surgical removal of bloodborne deposits of disseminated cancer in the lung is widely believed to benefit patients. **Tom Treasure** and **Martin Utley** analyse the evidence for pulmonary metastasectomy in sarcoma and call for a randomised trial

Patients with cancer are routinely screened to detect recurrence. The lungs are the commonest site of metastases, where they are readily detected by computed tomography, prompting consideration of their removal.[1] Operative risk is minimised by selecting fitter patients and using less invasive surgical techniques such as videothoracoscopy[2] or ablative techniques such as radiofrequency ablation. When surveyed, the majority of European thoracic surgeons reported performing metastasectomy often and with liberal indications.[3] However, the lung metastasectomy working group of the European Society of Thoracic Surgeons (ESTS) concluded that "although there was great experience in performing this surgery, the belief in its benefit relied on clinical case series and registry reports. Evidence fell well short of evidence based medicine standards and robust guidance could not be produced on this basis."[4] A missing component of the ESTS report was a review of the evidence for metastasectomy for sarcoma: one was commissioned but not delivered. Evidence for the practice in the literature is indeed lacking, as we found in a subsequent systematic review of clinical reports of pulmonary metastasectomy for sarcoma published in *BMJ Open*.[5]

Sarcoma occurs in a younger age group than the common carcinomas and metastasises to the lung in 50-60% of cases. These two features prompted surgeons at Memorial Sloan-Kettering Cancer Center, New York, to perform pulmonary metastasectomy from the mid-1960s, and in 1971 they advocated this surgery as the "treatment of choice" for osteogenic sarcoma.[6] The practice was taken up widely and is included in the National Institute for Health and Clinical Excellence (NICE) guidance *Improving Outcomes for People with Sarcoma*.[7]



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Surgeons operate to remove part of a diseased lung

What the evidence shows

Our review of clinical reports shows that the clinical decision is made on an individual patient basis, selecting those with fewer metastases, a longer interval since surgery on the primary sarcoma, and responsiveness to chemotherapy. Reference to any standardised criteria is uncommon. Patients with insufficient pulmonary function to tolerate the loss of the requisite amount of lung to clear macroscopic disease are excluded. Operation is usually by thoracotomy.

Pulmonary metastasectomy is intended to cure patients in whom the primary tumour has been removed and the lungs are the only known site of disease; the words "cure" or "curative" are used in seven of 18 reports and in NICE guidance. However, what is reported is five year survival, which ranges from 20% to 50%,[5] and it is wrong to assume that five year survival is a proxy for cure. Unusual among the reports is the frank statement: "True cure is extremely rare, the majority of patients eventually dying of the disease."[8] The same

Selectively operating on patients creates a false impression of the clinical effectiveness of pulmonary metastasectomy

conclusion emerged when the 22 patients reported in 1971[6] were reviewed after 10 and 20 years[9]: two were known to be alive without evident disease but most had died of recurrent sarcoma having had up to nine thoracotomies (mean 3.7 per patient).[10] Although the removed metastases may be the last remnant of cancer in a few patients, this is generally not the case.

Even though it is not indicative of cure, five year survival could still be a valid measure of benefit if few patients would have survived to five years without treatment. However, this is also not the case. Five year survival in the Thames Cancer Registry 1995-2004 was 25% and 15%, respectively, for bone and soft tissue sarcoma among patients with metastatic disease at the time of registration. Some of these patients will have had pulmonary metastasectomy, but it is unlikely to be an appreciable proportion. Furthermore, the reports we reviewed explicitly or implicitly attribute survival at five years to metastasectomy, even when chemotherapy and other treatments have been given.[5] In the absence of control data, quantifying the difference in survival among patients who have metastasectomy, and attributing it to the metastasectomy rather than selection for metastasectomy, is bad science.[11]

Selection

The degree of selection for pulmonary metastasectomy is rarely stated. Surgical follow-up studies start with the case records of patients who have had a pulmonary metastasectomy. Surgeons often do not report their selection and may be unaware of the extent of selection upstream of the surgical referral. In the seven reports that give data the proportion of sarcoma patients with pulmonary metastases having metastasectomy ranged from 5% to 88%; the proportion of all patients with sarcoma having metastasectomy was 1% to 36%.[5] These data are too variable to be meaningfully pooled and are likely to be based on differently defined denominators, but they allow plenty of leeway to select preferred patients.

Furthermore, the powerful effect of selection is disregarded. Seven studies used multivariate analysis to determine features associated with longer survival.[5] These include fewer metastases, longer interval since the surgical resection of the primary sarcoma, and the presence of necrosis caused by preoperative chemotherapy, all of which are likely to be associated with a better prognosis, irrespective of pulmonary metastasectomy. Selectively operating on patients with these features creates a false impression of the clinical effectiveness of pulmonary metastasectomy.[12] If you operate on patients who are more likely to survive, it is to be expected that they survive longer than those you did not operate on. Claims such as, "Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extend survival"[13] cannot be substantiated from uncontrolled follow-up studies.[11]

Searching for a more reliable source of evidence for current best practice, TT was referred to the European Osteosarcoma Intergroup report of 1067 patients with recurrent osteosarcoma in three randomised controlled trials. With specific reference to "survival after (repeated) resection of lung metastases" the report found "limited information on how the recurrences were treated" but concluded that "all patients were treated in experienced sarcoma centres and it is likely that all patients received the best available treatment for their recurrence."[14] The trial report does not give the criteria for pulmonary metastasectomy or any evidence for its contribution to patient outcomes.

Survival and palliation

The vision of managing cancer in a similar way to other chronic diseases is one justification for metastasectomy. The concept is that a cancer may run a chronic course during which the patient leads a good life, punctuated by clinicians doing things for them. Over 40% of patients with sarcoma have second or further metastasectomy operations, with some having 10 or more.[5] The surgery is given the credit for longer survival, but the presumed causal relation might be reversed: it is the patient whose disease is following a slower course who gets more operations, other interventions, and further cycles of chemotherapy.

If there is no proof of a survival advantage attributable to metastasectomy, is there palliative benefit? Removal of an intrathoracic space occupying lesion (for example, pleural effusion) improves breathing, so is that benefit seen after metastasectomy? In the reports we reviewed there was no record of respiratory symptoms or of before and after systematic measurement of respiratory function.[5] There is no evidence, but nor is there any indication in the texts that pulmonary metastasectomy is performed for respiratory benefit. Conversely it is poor lung function that calls a halt to further metastasectomy.

Case for a trial

Given the uncertainty in the evidence for pulmonary metastasectomy, a trial is needed to determine benefit. Although many argue against them, randomised controlled trials of surgery for advanced cancer can and are being done. Faced with an epidemic of mesothelioma, and hope of surgical cure by radical surgery, the Mesothelioma and Radical Surgery (MARS) trial was proposed in 2004.[15] A randomised trial was regarded as unnecessary by some, impossible by many, and unethical by both those strongly in favour of and those strongly against radical surgery for mesothelioma. It was not easy to recruit patients to the trial, but in the event 50 were sufficient to show that radical surgery was not of benefit.[16]

Similarly, the publication in the *BMJ*[17] of our doubts concerning effectiveness of pulmonary metastasectomy in bowel cancer focused attention on the need for the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial.[18] Bowel cancer is much more common than sarcoma and provides the largest number of patients for pulmonary metastasectomy.[19 20] PulMiCC incorporates an innovative trial design, retaining a large element of choice and self determination, intended to make random allocation tolerable for surgeons and patients. To achieve this PulMiCC employs two strategies. As with MARS, patients initially consent to join the study without commitment to randomisation. They are given full information about their condition, including video material informing them what is known and what is uncertain. Investigations are reviewed and data recorded by protocol. Only when there is clinical uncertainty about whether to propose metastasectomy are patients offered randomisation. MARS trialists who spent time in this uncommitted phase believe that it helped to achieve a more realistic understanding between the patient and the clinical team and about the uncertainty of benefit and that it was instrumental in acceptance of randomisation.

The second strategy introduced in PulMiCC is to explicitly recognise that in routine practice many patients with pulmonary metastases are deemed unsuitable for metastasectomy while others are advised to have it. Since there is a "yes" for some and a "no" for others there must be some notional tipping point, but exactly where is uncertain. When there is uncertainty among the members of the

multidisciplinary team responsible for jointly advising the patient, the treatment allocation is by randomisation. By the end of 2012 the recruitment to PulMiCC had passed the 100 mark, with more than 30 patients randomised.

There are real and imagined obstacles to randomised trials of surgery.[21] The MARS trial did not find that patients are resistant to randomisation. Doctors, however, are reluctant to admit that they do not know what would be best. Treatments that are likely to prove ineffective are justified as giving the patient "the benefit of the doubt." Would it not be better to resolve the doubt by finding out in which direction any benefit actually lies? A justification for giving further cancer treatment is often "to give hope," but that is all too often false hope; the harm done in the course of unavailing cancer surgery is under-reported and insufficiently considered.[22]

Another argument is that trials will have too few patients because of the predictable difficulty in recruitment, but we subscribe to Lilford's maxim "some unbiased evidence is clearly better than none."[23] Specialist centres exist for the care of rare diseases, such as sarcoma in its many forms. They provide access to clinical expertise but also the case volume for research. Collaborative research mechanisms have been used in oncological trials[14] but not to examine pulmonary metastasectomy. Maybe the first step is to spell out the degree of uncertainty and perhaps erode clinical confidence that we really know what we are doing, under all circumstances. The arguments in this article are deliberately framed for that purpose. We believe that better evidence is needed for the practice of pulmonary metastasectomy and that the PulMiCC trial design can be adapted for a sister trial in sarcoma.

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BMJ BLOG **Julian Sheather**

Judging our patients

I was recently talking to a bunch of GP trainers about the problems some of their trainees experience when they first open their consulting room doors to the wide and unrelenting world. Drug abuse, shattered families, violence and self destruction: all in a day's work for an inner city GP. And GPs are trained to respond to this without batting a moralising eyelid. They know that they must not pass judgment on the patients who come through their doors.

I have taught medical students and junior doctors for many years, and unless I am much mistaken most of them will be middle class. I realise that class is an increasingly slippery concept, but traditionally among the markers of the middle class have been certain values, such as thrift, investment in education and training, self discipline, wealth accumulation, and a certain emphasis on family and stability. These values—in themselves and in their parents—have no doubt helped students get to medical school. And these are the values that they will largely continue to hold dear as doctors. Is it any surprise then that a young trainee might experience disorientation when confronted with chaotic and self destructive lives? Any surprise that doctors might at times be tempted to conclude that behind some of the health problems lie moral ones?

Should doctors just go right ahead then and tell their patients what they think, in morals as well as in medicine? Well, no. Firstly because human beings are usually poor judges of others. In a complex world, and under pressure of time, we are likely to over-rely on our prejudices, particularly when threatened. Our knowledge of others, of what lies behind their choices, can also be scanty. There are also the likely consequences of moralising. Patients will simply stop visiting their doctors if they are going to be preached at.

There is a big difference between making judgments and expressing them. We make moral judgments almost as freely as we breathe. And if we suppress our judgments they are more likely to come out inadvertently, through all sorts of non-verbal giveaways. It is better by far to recognise that we are moral animals, that we have values, that we make judgments. If we know we are making them, we can at least ask ourselves if they are reasonable. And doctors who are familiar with their own morals are likely to be better placed to understand their impact on others. And, critically, in the consulting room they may be that little bit better able to draw a line between their private views and their professional obligations to patients.

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