Pulmonary metastasectomy: a common practice based on weak evidence

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ABSTRACT

The resection of secondary metastases from the lungs is a wide-spread surgical practice. Patients are referred from coloproctology teams to thoracic surgeons specifically for this surgery. What is the expected benefit? I have explored the rationale and searched the literature in order to present these patients with a well-informed opinion for their consideration. I find only weak evidence based on uncontrolled retrospective series which have been interpreted as showing a survival benefit. This has been extrapolated to policy and practice that do not stand up to scrutiny. The practice has never been subjected to randomised trial and I will argue that the present evidence is insufficient to justify the uncontrolled use of an intervention with inescapable short-term morbidity, permanent loss of function, and major cost implications. I propose ways in which the evidence may be improved, including a trial in the areas of most uncertainty.

KEYWORDS

Pulmonary metastasectomy – Benefit analysis

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The literature is largely in the form of retrospective case series, usually from single institutions but it includes registry data.^{1,2} There has been a tendency both in individual series and in the registry to consider all primary sites and even to report data on sarcomas, germ cell tumours and carcinomas together.⁵ There may be a special case to be made for individual cancer types such as germ cell tumours, sarcomas, and particular primary sites such as thyroid and kidney but, if so, the case must be made separately. It must surely be scientifically questionable to present outcomes without due attention to differing biology and behaviour of cancers. This cannot be explored if the results for different tumours are presented in a list of diminishing groups size in what I call ‘and a partridge in a pear tree’ fashion (Table 1).

As far as the common primary sites are concerned, there are fundamental differences in the current practice of surgery of metastases for the common solid cancer sites. The big three are lung, breast and large bowel.

1. The lung is my home ground. Removal of lung metastases from lung cancer is not attempted in clinical practice; the surgery of lung cancer is confined to attempting cure.⁴ Resection of the lobe or lung containing the primary with N1 lymph nodes with intent to cure is

deemed appropriate in 10–20% of cases and, to all intents and purposes, the question of resection of metastases within the lungs does not arise.

2. In the 1960s and 1970s, ever more radical surgery was performed for breast cancer including radical and super radical mastectomies as extensive as opening the chest to clear the internal mammary chain of lymph nodes. Breast cancer is now generally regarded as a systemic disease from the outset and lung secondaries are not a usual target. However, not all surgeons have accepted this approach.⁵
3. Colorectal cancer is the only one of these three common cancers where resection of metastases is performed with any frequency. Resection of liver metastases is now common and regarded as routine practice.^{6,7}

The resection of pulmonary metastases from colorectal cancer is the subject of numerous case series. We have found 73 reports comprising a total of 4815 cases ranging from four to 653 patients (median 43 patients; IQR 25–75). As with a recent review of resection of hepatic metastases,⁷ there have been no randomised controlled trials (RCTs). Data presentation of larger series is in the form of survival plots usually the output of Kaplan–Meier analysis. The

Table 1 The characteristic tabular display of cases in series from multiple cancer sites is reminiscent of *The Twelve days of Christmas*. It seems unlikely that any useful information can be gained by the inclusion of a single pancreatic cancer and a couple of thymic cancers. Pooling information on carcinoma, sarcoma and teratoma also is probably not useful

Twelve drummers drumming	Colorectal	26
Eleven pipers piping	Sarcoma	21
Ten lords a-leaping	Renal	11
Nine ladies dancing	Breast	9
Eight maids a-milking	Endocrine	9
Seven swans a-swimming		
Six geese a-laying	Teratoma	6
Five golden rings		
Four calling birds	Lung	4
Three French hens	Melanoma	4
Two turtle doves	Thymus	2
And a partridge in a pear tree	Pancreas	1

Clinical data from Poncelet *et al.*³

objective of treatment is, therefore, implicitly to improve survival and yet there are no formally constructed comparison groups. If a treatment is undertaken to improve survival, and reported in support of that belief, it would seem reasonable to put some effort into finding and presenting comparative data with similar rigour, and yet that has not been done as far as we can determine. There are rarely even any denominator data – that is to say a description of the case mix from which these cases are selected – and yet most authors place emphasis on the need to select patients carefully.

In the era of multimodality treatment, there is an argument to shift or expand cancer surgery from the notion of cure by total removal of the cancer to modification of the progress of the disease. The surgeon's role in the breast cancer team includes getting control of the primary site and obtaining detailed lymph node staging to guide other therapies. In sarcoma, there is perceived to be a place for surgery to control tumour volume and in germ cell tumours there is often a request to remove the residue after successful chemotherapy. But case selection in the reports of pulmonary metastasectomy primarily concerns operating on metastases only when the primary cancer is controlled and all the secondary cancer can be removed. The explicit intention is thus to complete removal and so to achieve cure.

When surgical cure is the goal, total eradication is required, and emphasis is placed on complete clearance:

that is R0 as opposed to R1 resection. As if it is a given that there is prolongation of life attributable to resection, more attention is paid to the method by which complete resection is best achieved. Surgeons have addressed the question 'how' without an answer to 'whether'. For example, some argue that video surgery is not appropriate because it does not permit bimanual palpation of the lung which reveals secondaries not seen on CT. A natural extension of the argument for complete bimanual palpation of the lung is that all pulmonary metastasectomy operations should include bilateral exploration. This would require sequential thoracotomies, median sternotomy or a clamshell thoracotomy. Systematic reviews of both these questions (VATS versus open⁸ and unilateral versus bilateral⁹) have failed to find an evidence-based answer. Rolle *et al.*⁵ report removing 124 lung secondaries in a bilateral operation in the belief that they had cleared them all down to the smallest and achieved R0 resection. One cannot help wondering how the authors knew there was not a yet smaller 125th deposit. If a requirement is R0 resection, necessitating bilateral open operations, this moves metastasectomy into a major league and harm is certainly caused.

The sad fact is that the Kaplan–Meier graphs of survival in all these papers concerning pulmonary metastasectomy move remorselessly downwards. More detailed statistical exploration of the survival data is usually in the form of multivariable analysis. In this way, factors associated with longer or shorter survival after pulmonary metastasectomy are identified. Those that emerge as significantly associated with longer survival are characteristically the disease-free interval following the primary resection, the level of carcinoma embryonic antigen (CEA) and differentiation and stage of the primary. (R0/R1 resection should not be in this list of predictors because it is a factor established after the operation, not in the pre-operative assessment.) Patients with several of these factors are then shown to survive longer than those without favourable features. These are then suggested to be the basis on which to select patients who will benefit from surgery. This is, of course, entirely circular; these are the factors that define longer survival and are related to the tumour not the surgery.

There is a recent detailed and thorough systematic review of liver resection for colorectal metastases.⁷ There are no randomised trials for the practice. In an exhaustive and expertly done systematic review, 529 studies were found; 470 were rejected from inclusion. Of the 59 retained, only two studies included all patients presenting with liver metastases and only three reported on all patients undergoing liver surgery. That is to say that the denominator from which the case series was drawn was specified in less than 1% of studies. Nevertheless, the authors regard the survival in these highly selected patients to be better than those normally associated with colorectal cancer. I have already

made the point that more care and attention should be given to the nature of the comparative data against which the surgical series is to be viewed. The authors are sufficiently confident that there is survival benefit that they see no need for an RCT now. An RCT is not the only basis for proof of efficacy^{10,11} but, in the absence of a greater treatment effect, I do not share their confidence. Far less can I accept that what is believed to be of benefit in terms of survival after liver resection necessarily applies also to the lung.

Some years ago, the editor of *The Lancet* faulted surgeons for the standards of their research liking it to comic opera.¹² Regrettably, things are not much better now and surgeons are also guilty of his more recent accusation – that we keep doing the same study over and over again without moving the question on.¹³ The 73rd series of pulmonary resection added no more knowledge and most of the 529 series of hepatic resections were not used by the systematic reviewers.⁷ What was the purpose of these reports? What was learned from them?

There is another area to consider when we operate – the relief of symptoms and the maintenance of quality during the patient's remaining life time. Simmonds *et al.*⁷ found no studies reporting co-morbidity, quality of life, or cost effectiveness of liver resection and nor have we for pulmonary resection for secondary cancer. In the thoracic literature, there is only scant mention of lung function and yet we know that loss of lung parenchyma causes an inevitable, and irrecoverable, loss of lung function.

Finally, there is the claim that patients benefit psychologically from removal of cancer. It is likely that there is a basic desire to rid ourselves of cancer but surely, in a rational discussion, this must be put in perspective and properly analysed. If a patient is clearly informed that there is no survival or symptomatic advantage to be gained from an operation, and only harm could ensue, would the patient still have the operation for psychological reasons? I would give more credence to this tenet if there were any measures of psychological well-being in any reported series or if there were mental health experts amongst the authors. The argument for psychological benefit was challenged by Aberg and colleagues^{14,15} years ago and remains insufficient to convince me to perform a thoracotomy for a patient's mental health.

Guidance available at present

In the *NHS Cancer Plan 2000*, the UK Department of Health determined 'from 2001 (NHS Trusts) put in place cancer site specific teams and ensure all patients are reviewed by them'.¹⁶ This recommendation that all patients with cancer have their diagnosis and management plans reviewed in a multidisciplinary team meeting has been widely implemented.

There are good reasons to believe that this is in the best interests of cancer patients.¹⁷

Lung nodules have many causes and their investigation, and the management of those that are revealed to be malignant, is part of the work of the lung multidisciplinary team. An important reminder is that any solitary lung nodule must be considered as a possible primary lung cancer; just because there is a history of cancer elsewhere does not mean metastasis can be presumed. On occasions, the only way of being sure is after resection. Of necessity, we also review patients with pulmonary nodules believed or known to be metastases from other cancer sites. The lung multidisciplinary team deals with all cases of lung cancer and in the initial investigation of other suspected intrathoracic cancer, whether primary or secondary. Lung, pleura and mediastinal lymph nodes are amongst the most frequent sites for secondary cancer but the first task is to determine whether the presenting problem – nodule(s), pleural thickening, effusion or lymphadenopathy – is a manifestations of cancer, and whether it is primary or secondary.

Patients with pulmonary metastases from colorectal cancer are increasingly referred to thoracic surgeons with a request for excision of the secondary cancer. This is in accordance with the recommendations included in the 2004 UK NICE Guidance on Cancer Services, *Improving outcomes in colorectal cancer*.⁶ The guidance to the colorectal multidisciplinary team is that its process should include referral of patients with metastases, confined to limited areas of the liver or lung, to specialised multidisciplinary teams for an opinion on their management. The anticipated benefits are set out as follows: 'Surgery for patients with metastases confined to the liver or lung can be curative when carried out by specialists with experience of this type of work. Although such resection is only appropriate for a minority of patients, it can improve five year survival from close to zero to over 30%.' The reference cited in support of this is a 1994 paper in *The Lancet*,¹⁸ which is a case-series analysis about untreated liver metastases. Whether or not coloproctology multidisciplinary teams regard this as sufficient evidence for the removal of liver metastases, it is insufficient evidence for the removal of lung metastases since the cited paper contains no data about patients with lung metastases and no surgical results.

How might we learn more?

We plan more detailed analysis of survival data for populations of patients like those in whom resections are carried out. This will require meticulous work and mathematical modelling which will be undertaken by experts. Suitable series are not easy to find but we believe that we can improve upon the broad-brush citing of historical survival data.

Table 2 The PICO for a trial design of pulmonary metastasectomy

PATIENTS	Colorectal cancer where benefit is uncertain
INTERVENTION	Induction chemotherapy Complete surgical resection Any other management
COMPARISON	Induction chemotherapy Any other management
OUTCOMES	Survival and quality of life

Better still would be a randomised trial. The authors of the recently published systematic review opine: 'Randomised trials comparing metastasectomy versus non-surgical treatment modalities are not possible now'² which is not only defeatist but unacceptable in a scientific era.¹² RCTs are indeed difficult in surgery but not impossible. Witness the Mesothelioma and Radical Surgery (MARS) trial which was confidently predicted by experts in the field to be impossible to do. It is up and running, randomising patients.¹⁹ Beyond the primary purpose of addressing the

question – does radical surgery confer benefit over the other aspects of multimodality treatment? – it engenders a more questioning and evidence-based culture for all who care for these patients whether in or outside the trial.

In mesothelioma, as with metastasectomy, the difficulty of discerning any benefit of surgery is compounded because resection is often combined with a range of other therapeutic strategies, including predominantly chemotherapy. So, if there are perceived improvements, particularly since chemotherapy has been a therapeutic adjunct, is the surgical component the beneficial factor?

In designing a trial, a good exercise is first to define the PICO, which is an acronym for the essentials of a trial design (patients, intervention, control and outcome; Table 2) The most difficult part may be to define a group of patients where randomisation is possible.

Consider the following two scenarios:

Scenario 1

A single metastasis appears, 4 years after resection of the primary colorectal tumour when all had seemed clear on all intervening investigations. The patient is fit and the metastasis is easy to remove from the periphery of the lung with minimal access.

Scenario 2

An X-ray taken on first follow-up a month after colorectal resection, which was poorly tolerated, shows metastases in every pulmonary lobe totalling about twenty.

Table 3 Survival model derived from Kanemitsu *et al.*²⁰

Mets	Histology	CEA	Median survival (years)	3-year survival (%)
1	Well differentiated	< 5	7	75
1	Moderately differentiated	< 5	5.5	65
2	Moderately differentiated	< 5	4	60
2	Moderately differentiated	50	2	25
3	Moderately differentiated	50	1.8	20
3	Moderately differentiated	100	1.2	10
5	Moderately differentiated	100	1	5

Kanemitsu and colleagues offer a model based on five factors:

1. Presence of mediastinal nodes (unfavourable)
2. Presence of extrathoracic disease (unfavourable)
3. Number of lung metastases (fewer the more favourable)
4. Histology (better differentiation more favourable)
5. CEA (the lower the more favourable)

In this table, examples were created from the rather complex model to illustrate seven instances. The first two have been excluded because the results are so poor that they would fail consideration for most surgeons.

All of the multidisciplinary teams I know of would offer to resect the single metastasis in the first scenario but I know of none that would operate to remove the multiple metastases in the second scenario. It follows that every team must have a zone of uncertainty, if they can make a decision to operate or not under different circumstances. Interestingly, this uncertainty can be variously denied or disguised. The old adage of the surgeon 'often wrong but never in doubt' applies here but if the group are prepared to test the case against the model of Kanemitsu *et al.*,²⁰ for example, there must be a level at which the belief for benefit for the very few must be so small in relationship to the harm done to all, that it is not right to operate (Table 3). Each multidisciplinary team could identify scenarios where, for them, there is uncertainty as to the benefit of resection. Where there is uncertainty, unbiased allocation is possible and as rational as either alternative. The informed public understand that.²¹ It may be the doctors who find it more difficult.

Conclusions

Taking an overview, I conclude that even a generous reading of the literature on the subject indicates: (i) a lack of clarity as to the objectives; (ii) the rationale for removal of metastases is insecure; and (iii) the evidence available does not address the question of whether benefit exceeds harm.

These are bold statements and run counter to much that is practiced but seemed to me to be a suitable subject to address in the Tudor Edwards Lecture which honours the memory of one of the founders of the practice of thoracic surgery. My mathematician colleagues, I discovered, believed that because metastasectomy operations are done, there must be a good reason. Let us just burst that belief bubble. In other times, doctors as intelligent, as rational and as compassionate as ourselves have done things that we do not do now, including blood letting, cupping, organopexy, colectomy for constipation, industrial scale tonsillectomy in children, ever more radical surgery for breast cancer, and bed rest for everything. These are not now practised. It follows that doctors of the future will not do all the things we do now, but we do not know which interventions they will look back on as unavailing. But you can be sure that there will be some.

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