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Review article

Analysis of pulmonary metastasis as an indication for operation: an evidence based approach

Torkel Åberg
Tom Treasure*

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*Corresponding author
Tom Treasure MS MD FRCS FRCP
Clinical Operational Research Unit
University College
4 Taviton Street
WC1H 0BT

Phone 00 44 79 57 16 87 54
Fax 00 4412 33 74 03 78
E-mail: tom.treasure@gmail.com

Introduction

Pulmonary metastasectomy is analysed in this paper according to the rules of Evidenced Based Medicine. Our knowledge of metastasectomy lacks several crucial factors necessary for the tenets of EBM: survival without surgery in this special group of patients; knowledge of the denominator from which the cases are selected; and the biological nature of the individual tumour. If metastasectomy were introduced today as a new treatment, it would not be accepted.

Our analysis provides an alternative interpretation of five-year survival rates of 40% after metastasectomy as being a result of selection of the patients at the benign end of the continuous spectrum of malignancies. It is therefore a statistical illusion. Given the many variables and the long time course in many patients with or without metastasectomy, the effect of surgery can only be resolved by a randomised control two armed trial, where the outcomes between an unoperated group (the natural history) and an operated group (the natural history modified by treatment) are compared.

Absence of knowledge is readily accepted by many patients if candidly and respectfully explained and so a randomised trial is possible, appropriate and acceptable to sufficient patients. In order to shed light on whether there is truly a survival benefit from metastasectomy a randomised trial has been started. Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) has so far recruited 86 randomised patients and is open internationally. It is funded for a further five years. Interested groups are invited to join the trial.

An evidence based way of thinking

Evidence Based Medicine has provided a logical way of defining the 'indication' for treatment. An 'indication' as used in medical English is the base around which we decide to recommend treatment to patients. It can be said to be the centre of the doctor's professional duty: to identify as unequivocally as possible the indication for treatment. To decide on an indication is to influence the fate of the patient. The indication has therefore to be surrounded by stringent and quality assured rules.

The ideals of Evidence Based Medicine have been of great value to *patients* but at the same time we must not forget that the evidence has to be individualised. Indications for treatment may be reached from various forms of evidence and encapsulated in clinical guidelines or, when we are less certain, consensus statements. Clinical guidelines[1] seek to make irrefutable recommendations, based on the latest and best available evidence while consensus statements are based on opinions and are more tentative. Nevertheless, we cannot expect even the most secure evidence based guidelines to be implemented in 100% of patients. The guidance has to be personalised according to the treating doctor's view of the best interests of the individual patient.

The ideals of EBM have also been of great value to *doctors* who have to advise for or against treatments. This can only be done conscientiously when we are able to point to evidence.

The ideals of EBM have been of value to *society* so that we are all spared the distress and the cost of needless treatments. The introduction of new drugs and the indications for their use are now subject to stringent rules which must be adhered to. Surgical operations should be just as carefully considered. Society should not be asked to spend its precious resources on

ineffective treatments. The nation's nurses and hospitals are a shared resource; the doctors as the main drivers of costs in a health system must be responsible for their proper use.

Bringing the evidence base to the individual

The phrase Personalised Medicine came into use, as if in opposition to EBM, but it is a false dichotomy. The tightest evidence based guideline should be overridden for some patients. That is to say they are 'personalised'. But with respect to lung metastasectomy there are no clinical guidelines. The European Society of Thoracic Surgeons Lung Metastasectomy Working Group (LMWG) considered producing guidelines but concluded '… the level of evidence to support current practice is too low to set firm recommendations to the members of ESTS. In the absence of a randomized controlled trial looking at the effectiveness of pulmonary metastasectomy on survival and quality of life, it is unlikely that the current practice will ever be influenced'.[2] More recently the Society of Thoracic Surgeons has searched and not found evidence of the kind on which 'trustworthy' clinical guidance can be based. The result is that there are no guidelines, in Europe or the US because there is no trustworthy evidence base.[1]

The leaders of ESTS LMWG directed readers to the PulMiCC trial proposal (Pulmonary Metastasectomy in Colorectal Cancer).[3] That was more than five years ago. Since then there have been many further publications but they do not introduce new information based on better evidence. They come to the same conclusions as were reached by the early follow-up studies in the 1970s and the registry data in the 1990s. In this article we will go back to basics and examine the sources of evidence on which we might build the indication for metastasectomy.

The importance of knowing the 'natural history' of the condition

In the very earliest days of surgery for congenital heart disease Maurice Campbell (1891-1973) made the important decision that the large number of patients they had seen at Guy's Hospital with congenital heart disease, untreatable up to that time, should be categorised in as much detail as possible. He asked that their clinical course be meticulously recorded. Without that record he argued, future cardiologists and surgeons would never know how the newly introduced operations had altered the 'natural history'.

What is the equivalent 'natural history' of lung metastases? Five year survival of patients with lung metastases is commonly assumed to approach zero. Is this a realistic estimate? It was contradicted by Åberg's finding reported in 1980 of a five year survival of 25% for unoperated patients, similar to that of contemporary patients who had lung metastasectomy.[4] The data were few (3/12) and the confident limits are wide (6%-57%) but they do not include zero.[5] A realistic estimate of the natural history of the disease is an absolute requirement. For present day patients with lung metastasis we still do not have that essential information.

Cancer registries

There are registry data which provide the natural history of patients with cancer usually divided by stage. In Tables 1 and 2 we show cancer registry data for survival of all patients with colorectal cancer and sarcoma in the worst category in the registry, designated Stage 4. This includes only patients who already had metastases at the time of diagnosis. The

important piece of information is that even with metastases at presentation (and these are the minority in clinical series) there is a non-trivial number of five-year survivors. It is of the order of 10% for colorectal cancer in the cancer registry. Therefore the number for whom survival can be attributed to lung metastasectomy is already well short of the 40% that is generally inferred from follow-up studies. Survival rates of 40% after lung metastasectomy are compatible with selection of the most favourable patients with no beneficial effect from metastasectomy.[6;7] For many diseases the cancer registry survival data have improved decade by decade so the difference attributable to metastasectomy will have narrowed. We hope that improved survival is a reflection of better treatments and effective operations, but there are other statistical factors which we will now consider.

The illusion of improving results

Lead time bias. Detection of metastases much earlier can now be achieved by more available health care and more sensitive diagnostic tests. If the diagnosis is made one year earlier the recorded survival of the patient will be one year longer. This is called lead time bias and it creates an illusion of improving outcomes simply because the stop watch was started sooner.

Stage migration. With the introduction of new method**s** of detection we have been able to stage patients more precisely. Some patients diagnosed as Stage I lung cancer are now classified as Stage II because we can now see previously undetectable lymphatic involvement. This is called stage migration. Similarly, better detection of mediastinal node involvement with lung metastases**,** and the exclusion of these patients, produces a group for metastasectomy with a better natural history. Any difference in observed survival would be due to better selection not the metastasectomy.

Better detection or more exlusions? With CT we were able to detect lung metastases. With the addition of PET to CT, some patients with lung metastases are now seen to have unsuspected sites of cancer elsewhere in the body. This results in more exclusions which has the effect of narrowing down the selection of patients in whom metastasectomy is 'indicated'. The survival results will inevitably appear to be better. Higher five-year survival in this more highly selected group may be a consequence of selection rather than metastasectomy.

Efficacy and effectiveness

There is a distinction made in EBM between 'efficacy' and 'effectiveness'.[8] Unfortunately the two words are more or less interchangeable in every day English but in the language of EBM, efficacy is used to for interventions that can be seen 'to work'. So if a surgeon removes a solitary lung metastasis and the pathologist reports cancer free margins the operation has efficacy; the metastasis has been removed. Whether the operation is 'effective' in achieving the desired clinical outcome, which is to improve survival, the pathologist cannot say. Even after five years patients may die of their same cancer and the metastasectomy can then be seen to have been ineffective as a means of cure. The many variables and the long time to reach the outcome, means that clinical effectiveness of lung metastasectomy does not meet the criteria for being provable on observational data alone.[9]

When can we trust observational data for evidence that a treatment is effective?

There are many treatments where repeated observation and experience were sufficient proof for a treatment to become established. [9;10] Surgeons do not hesitate to relieve tension pneumothorax or to retrieve an inhaled object obstructing the trachea. Rightly no one asks them for RCT evidence. Cataract and hip surgery, and the relief of mitral and aortic stenosis,

all entered practice without RCTs. In these examples the surgeon deals with a single, clearly evident cause of the patient's problem which is then promptly relieved by a mechanistically rational intervention. If these principles are used to test the effectiveness of lung metastasectomy, it fails the test. There are multiple factors involved and the time scale is measured in years so attribution of the patient's survival at any time point up to and beyond five years cannot unequivocally be attributed to that surgical action.

It is worth noting that for treatments which can be seen to effective by observation alone[9] the more severe the problem, the greater is the benefit to the patient. It is for that reason that we are prepared to observe a small pneumothorax or a mild degree of aortic stenosis: it is for the severe cases that we know we should intervene. This is in contrast to lung metastasectomy. Patients selected for metastasectomy are the least severely affected among a heterogeneous population: they have fewer metastases, longer intervals to their appearance, and progress more slowly. Under those circumstances EBM does not allow us to attribute the patient's survival at any given time point to the lung metastasectomy, without control data.

We must remember that lung metastases are rarely the proximate cause of death. Patients in whom the only site of cancer is the lung metastasis have a good prognosis for survival at least in the short term. They are not likely to die 'any time soon' so one year survival data are clearly meaningless in this context. There is an argument that we must hurry to resect a lung metastasis because it in turn may metastasise onwards to the mediastinal nodes and from there disseminate. However, as we will see this is not the basis on which the practice of metastasectomy is founded. On the contrary, results are known to be better if metastasectomy is delayed during a period of observation.

The traditional approach: surgeons' follow-up studies

It is understandable for a surgeon to want to remove a malignant tumour. Tumours were seen as a 'surgical' disease. The slogan 'when in doubt, take it out' is familiar to all surgeons. The first formulation of the indications for metastasectomy was that there should be a solitary or very few metastases; the original tumour should have been radically resected; and that the patient has the pulmonary reserve to withstand thoracotomy and the necessary loss of lung parenchyma to clear all the disease. These requirements were implicitly understood and were the basis of Thomford's criteria set out fifty years ago.[11]

It was also understood that there should have been an interval of time since the primary resection. This often included a further period of observation after the metastasis became evident to ensure that there was no rapid progression or residual cancer elsewhere. Systematically reviewing the many follow-up studies, this interval was found to be on average 1-2 years since the primary surgery in cases of sarcoma[12] and three years for colorectal cancer.[13] This meant that only a few of all patients with lung metastases met the criteria. Turney and Haight's paper from 1971[14] is an example that was influential as the practice became established.[15] The overall five-year survival was 40% but the data were from 68 patients including children, operated on between 1939 and 1963, with a very wide range of cancer types. That is an average of fewer than three patients a year. Studying this paper again in preparation for writing our paper it is seems to have been widely misquoted and perhaps given more authority than, with hindsight, it deserved.

Follow-up studies, although they are the commonest form of 'evidence' for surgery, have several insurmountable weaknesses.[16] In the context of lung metastasectomy there are two recurring problems illustrated by this study. One is the difficulty in determining the degree of selection. On average only one patient had a metastasectomy in a four month period.[14] If they found patients for metastasectomy that infrequently, how large was the denominator from which the patients were selected? A second is the absence of any control group. These concerns led to Åberg's study of patients eligible for, but who did not have, lung metastasectomy. He found that some of them survived five years without metastasectomy.[4]

Registries

The major landmark work in this field is the International Registry of Lung Metastases (IRLM) published in 1997.[17;18] The analysis of 5206 patients, meticulously carried out and clearly presented, irrefutably showed that the favourable factors for survival were (i) an interval since primary resection of greater than three years and (ii) a solitary metastasis. The IRLM authors choose their words carefully. They call these *prognostic* factors which is indeed correct. These are general prognostic features for cancer survival irrespective of treatment rather than being predictive of a beneficial effect of metastasectomy.[19] The IRLM authors were also quite clear in their recommendation for further work. In their view the registry would 'define areas of uncertainty concerning surgery and other therapeutic modalities to be explored by prospective randomized trials.'[18]

Welcoming the registry as 'the major scientific initiative during the last 20 years Åberg commented that the 'inclusion in the registry of the probably few patients who abstain from operation after being advised to have it would add to the value of the registry.'[15] That would have provided the critical missing piece of information: the unoperated survival for patients who are similar to those having metastasectomy. That is the 'natural history' as outlined already.

There is another important registry study in which data were collected prospectively to capture practice as completely as possible. Spanish surgeons collected data on 543 patients representing about 60% of all lung metastasectomy operations in their country in a two year period 2008-2010.[20] The starting point was patients who had a histologically confirmed metastasectomy. The opportunity to capture the intention- to-treat outcomes was lost as a consequence, as was the survival of patients declining metastasectomy. From this two year collection of national data, we can deduce that fewer than 3% of patients with colorectal lung metastases have metastasectomy. This is consistent with other database analyses in which this information can be estimated.[20] If we put this high level of selection alongside our knowledge of prognostic features for long survival, it becomes less impressive that follow-up studies include 40% five-year survivors.[6;7]

Understanding the biology of the cancer: tumour doubling times

Nodules in the lung characteristically show up clearly as opacities surrounded by radiolucent lung: a white on black measureable image. Their doubling times can be calculated. This has been done for metastases in the CT era. Doubling times varied from 22 to 930 days. [21] A calculation can be made, based on doubling times, of how long it takes a microscopic focus of cancer to become visible and how much further time it takes for a radiologically visible tumour to reach a lethal volume.[22;23] At the upper end of the distribution are indolent cancers which are not going to be life threatening within the likely lifetime of the patient. [Fig.1] The simple measure of repeating the CT scan at an interval and thus getting a closer

knowledge of the patient´s disease would be one step further in the principles of Personalized Medicine but operating on those who show little increase in size is one way of selecting the natural survivors. It would increase the number of observed five-year survivors in a surgeon's metastasectomy case series without making any actual impact on survival of the patients presenting with metastases.

Doubling time as a means of selecting patients for metastasectomy was explored in patients operated on from 1960 to 1970. In 113 patients, doubling time was found to vary from 18 to more than 360 days by Joseph and colleagues. Of these patients 24 had metastasectomy and 89 did not. Patients with doubling times of less than 40 days died within two years whether operated on or not. Patients were investigated and the metastases re-measured after three months. They operated on those with lesser rates of growth. (To do that is of course to contradict any imperative to remove them as soon as possible before they metastasise onwards.) The consequences was that a subset of 11 patients with doubling times >40 days, who had a deliberately inserted additional period of observation, *and* who had metastasectomy all survived for five years.[24] Patients with the slowest growing metastases defined their own 'survivability' a term which has been used before in the context of lung metastasectomy.[25]

Where have we come to?

These various considerations lead us to believe that the attribution of survival of patients after five years to the metastasectomy operation is predominately a mathematical illusion with an element of wishful thinking.[16;26] If we just rely on the data themselves, a meta-analysis of 25 well reported follow-up studies of nearly 3000 patients showed that long survival was improbable if there was more than one metastasis and an interval of less than three years. The conclusion is essentially the same as that reached in the follow-up studies in the 1970s,[14] confirmed with larger numbers by the IRLM in 1997,[17;18] and demonstrated again with a more sophisticated meta-analysis in 2013.[27] Nevertheless the surgeon authors concluded '… it seems currently unfair to deny surgery for those patients with two to four lesions.'[27] One wonders what is the point of repeating the same analysis and reaching an ever more certain statistical result and then overriding it with the emotionally laden words 'unfair to deny'?

We draw an alternative conclusion. It seems to us not only unfair to continue to offer operations without a realistic prospect of benefit to our patients but it is irrational to hold a belief that is so far at odds with the evidence. Why not tell the patient with four metastases the truth: in this and other analyses [28] metastasectomy has been shown to not provide benefit?

What is happening now is that stereotactic radiotherapy (SABR/ SBRT)[29] and image guided thermal ablation (IGTA)[30;31] are presumed to be effective based on the claims for surgical metastasectomy. They are being offered as a less invasive way of doing the same job. They are being introduced without trials, resting on no more than surgical practice, itself without evidence from control data.[32-34]

Where are we heading?

There are educational and practical problems ahead. As a result of better selection, less traumatic surgery or adjuvant treatment, or for a combination of these reasons, 'improved' survival rates of 40-50% five year survival after lung metastasectomy (taking colorectal cancer as an example) are now common around the world. As we become able to exclude the

more aggressive carcinomas with, for instance, genomic analyses we might see even better five-year survival rates perhaps to 70-80%. That would further fortify the belief in the effectiveness of metastasectomy but it would be a statistical mistake.[16]

New evidence from controlled trials

There is new evidence that raises a serious challenge to the practice of metastasectomy. In the case of colorectal cancer, the commonest indication for lung metastasectomy, there is a belief that patients who have had potentially curative primary resection should be monitored in order to detect metastases as early as possible so that they can be resected. There has been a succession of recently published randomised controlled trials aimed at advancing detection of metastases with the intention to remove them. Increased intensity of monitoring does advance the diagnosis compared with current standard care. The surprising finding is that more intensive monitoring does not lead to improved survival. This has been found repeatedly in multicentre randomised controlled trials. It seems counterintuitive: surely earlier detection allows for treatment which must improve survival? That has not been the case.[35-39]

The PulMiCC trial: Pulmonary Metastasectomy in Colorectal Cancer.

Following the tenets of EBM the question about effectiveness of metastasectomy is one that requires a randomised trial to obtain an answer.[10;40] An RCT has the virtue that it ensures that both the known and *unknown* confounding factors are similar in both arms. It is surpassed in scientific value only by meta-analyses of several randomised controlled trials. A treatment with as much uncertainty as lung metastasectomy would not now be introduced into practice without RCTs. An RCT is indeed necessary.

PulMiCC is based on existing clinical practice in which a minority of patients with lung metastases from colorectal cancer are selected for metastasectomy while the majority are not. [Fig.2] The trial design is built on the logically inescapable fact that on the multifactorial spectrum of disease there must be a zone where there is uncertainty if metastasectomy is offered to some and not to others.[40] Patients should be informed about that uncertainty. Even if it is uncomfortable to admit it, we owe it to patients to tell them when there is no firm knowledge.[41] If the uncertainty is made explicit, random assignment is an understandable course of action for many patients. After several years of preparation, including involvement in the ESTS Lung Metastasectomy Working Group, the randomised trial Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) was launched in 2011. It has successfully completed a pilot phase and shown feasibility. To date there are over 420 patients in the PulMiCC cohort and more than 80 patients have been randomised. PulMiCC is funded to run for the next five years. Patients randomly assigned to the interventional arm may have surgery or ablation according to clinical judgement of the most suitable method. Those assigned to not have an intervention are monitored and can be treated in any way the clinical team considers appropriate. PulMiCC has now run for four years and is is open internationally. Interested groups are welcome to join the trial.[42]

The patient's view

The carefully selected patient with a lung metastasis with proven favourable features, can expect a fairly long survival, not months but years, *with* the metastasis. The metastases that can be seen and removed are very unlikely to be the eventual cause of the patient´s death. If metastases are symptomatic that might justify treatment to relieve the symptoms but in general they are asymptomatic and remains so, rarely contributing to symptoms or distress near the end of life. These facts should be shared with the patient.

In justification some surgeons say they ‘give the patient hope’; giving *false* hope is not good medical practice. Properly and sympathetically informed, and perhaps by someone other than the surgeon, many patients would be grateful to be spared an operation which will not benefit them. The time taken out of the last year or two of their lives can be spent in better ways than undergoing surgery and recovery. Surgeons are quick to point out that there is very low risk associated with metastasectomy. The perioperative mortality is not a point at issues anywhere in our analysis. Dr Hahnemann (1755-1893 introduced highly ritualised dilution to vanishing concentration of the drug to spare his patients therapies with high toxicity. The doctrine of homeopathy of homeopathy was based on reducing risk. Metastasectomy in expert hands carries low risks of death and morbidity but surgery should only be done for a demonstrable benefit. Justifying ineffectual treatments because they do little harm is not cogent reasoning. Investigations and interventions have a cost, they take up doctors’ and patients’ time, and they carry a risk of harm, however infrequent.

However, we know that the prospect of living with a metastasis may be intolerable for some patients. After comprehensive information about the nature of the disease and the relative prospects of life with or without a metastasis, the patient may still insist on an operation. The indication then becomes their psychological well-being. We are surgeons, not psychiatrists or psychologists, and should be cautious about such a recommendation without expert evaluation of the patient’s mental health. But our aim is not to completely rule out lung metastasectomy but to base the indications on rational thinking, the patient´s needs, and an explicit interpretation of the evidence. Maynard Keynes famously wrote: "When my information changes, I alter my conclusions. What do you do, sir?" Our current position is based on consideration of all the evidence that we are aware of and if this evidence changes we would change our minds.

406 Table 1. Colorectal cancer. Five-year survival data of patients with metastases at
407 registration.

Era	Stage 4 cases	Five-year survivors	%5YS
1980 to 1989	7205	501	7.0
1990 to 1999	9767	756	7.7
2000 to 2009	12831	1519	11.8

408

409 Legend to table 1. Thames Cancer Registry cases registered as having metastases from
410 colorectal cancer at the time of diagnosis in three decades from 1980 to 2009. It is unlikely
411 that many of these patients underwent lung metastasectomy. For example the most active
412 group in the Thames region at the time reported 29 patients having lung metastasectomy for
413 carcinoma of any type in an eight year period (<4 per annum).[43] These five year survival
414 figures provide an order of magnitude for the survival of registered patients with metastases
415 of nearly 10%. If the most favourable quartile were identified as lung metastasectomy
416 candidates but not operated on (10/25=0.4) about 40% survival would be observed.[6;7] The
417 colorectal cancer patients have usually not had metastases at the time of the primary resection
418 and have already survived longer than 2-3 years from the time of diagnosis before lung
419 metastasectomy. The authors acknowledge Henrich Møller for providing the data for
420 inclusion in these tables.

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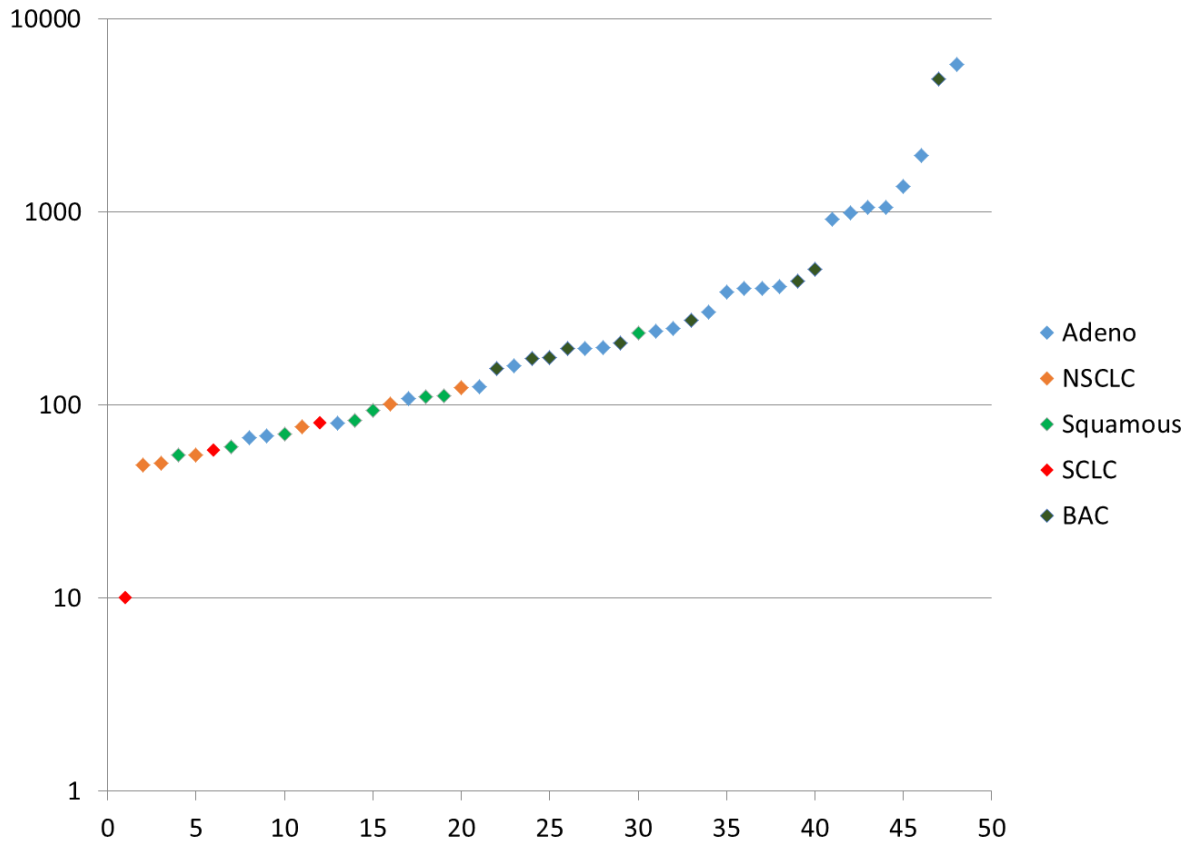
Table 2. Sarcoma. Five-year survival data of patients with metastases at registration.

Era	Bone	metastasised	Five-years survivors
85-94	281	84	19.8
95-04	310	94	24.8
	Soft tissue	Stage 4	
85-94	2072	398	12.57
95-04	2145	536	14.92

Legend to table. Thames Cancer Registry cases registered as having metastases from bone or soft tissues sarcoma at the time of diagnosis in two decades from 1985 to 2004. The group designated to manage sarcoma in the Thames region at the time reported 43 patients having lung metastasectomy for carcinoma of any type in an eight year period (about 5% per annum)[43] so these five year survival figures cannot be attributed to lung metastasectomy. Long survival after lung metastasectomy may reflect selection of patients with favourable natural history of survival.[12] The authors acknowledge Henrich Møller for providing the data for inclusion in these tables.

Legend to the figure

These data are from a study of the change of volume over time of nodules detected in a lung cancer screening project.[44] The cancers are distributed on the horizontal axis going from shortest to longest by doubling time in days (Vertical logarithmic scale). All were removed and the histology was established. We have retained the original authors' terminology. It can be seen that adenocarcinoma tended to have much longer doubling times than squamous and small cell lung cancer. The cancers to the right would have taken many years to represent a threat due to the bulk of cancer and would have been unlikely to cause the death of the patient. The patient would have died with the cancer, long before it caused any life-threatening effect. Similar distributions are seen for lung metastases and the same conclusion might be drawn.[21]



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