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Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data

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Contributorship statement

- Tom Treasure instigated the study, reviewed and revised data extraction, created the data tables, did a critical textual review, wrote the first draft and edited all subsequent drafts.
- Francesca Fiorentino did the initial data extraction and created the final versions of the figures.
- Marco Scarcie did the initial literature search and subsequent updated literature searches.
- Henrik Moller was responsible for identification, extraction and analysis of ed and extracted comparative data from the Thames Cancer Registry.
- Martin Utley oversaw data analysis, interpretation and presentation.
- All authors reviewed the manuscript at each stage and have approved the submitted version.

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We are willing to share data.

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Objectives: Sarcoma has a predilection to metastasis to the lungs. Surgical excision of these metastases (pulmonary metastasectomy) when possible has become standard practice. We reviewed the published selection and outcome data.

Design: Systematic review of published reports that include survival rates or any other outcome data. Survival data were compared with those in a cancer registry.

Setting: Specialist thoracic surgical centres reporting the selection and outcome for pulmonary metastasectomy in 18 follow up studies published 1991-2010.

Participants: Patients having one or more of 1357 pulmonary metastasectomy operations performed between 1980 and 2006.

Interventions: All patients had surgical pulmonary metastasectomy. A first operation was reported in 1196 patients. 43% of 1357 patients had subsequent metastasectomy, some having 10 or more thoracotomies. Three studies were confined to patients having repeated pulmonary metastasectomy.

Primary and secondary outcome measures: Survival data to various time points usually five years and sometimes three or ten years. No symptomatic or quality of life data were reported.

Results: 34% and 25% of patients were alive five years after a first metastasectomy operation for bone or soft tissues sarcoma. Better survival was reported with fewer metastases and longer intervals between diagnosis and the appearance of metastases. In the Thames Cancer Registry for 1985-1994 and 1995 to 2004 five year survival rates for all patients with metastatic sarcoma were 20% and 25% for bone, and for soft tissue sarcoma 13% and 15%.

Conclusions:
The 5 year survival rate amongst patients who have pulmonary metastasectomy is higher than that observed among unselected registry data for patients with any metastatic disease at diagnosis. There is no evidence that survival difference is attributable to metastasectomy. No data were found on respiratory or any other symptomatic benefit. Given the certain harm associated with thoracotomy, often repeated, better evidence is required.

Introduction

Pulmonary metastasectomy is a well established component in the management of sarcoma. Metastases may be confined to the lung where, surrounded by air containing lung, they are readily detected on radiographs and are usually surgically accessible. The Cooperative Osteosarcoma Study Group (COSS) found that, of 202 patients who had metastases at diagnosis, 81% had lung metastases and 62% only lung metastases.[1] In an analysis of three European Osteosarcoma Intergroup (EOI) randomised controlled trials of chemotherapy, of 564 patients who had recurrence, 307 (54%) had metastases only in the lung.[2] Osteosarcoma particularly affects the young, who are better able to withstand surgery and, if they can be cured by eradicating the disease, or their survival is substantially lengthened, there are potentially many years of life expectancy to be restored.

The decision to perform pulmonary metastasectomy is usually now made by specialist sarcoma teams and is based on factors such as the interval since surgery, the number and rate of growth of metastases, and their response to chemotherapy. The surgical approach may be videothoracoscopic or by thoracotomy, and surgery may be through staged lateral thoractomies or bilateral through an anterior approach. The pulmonary resections are also "individualised" depending on the location, size and number of metastases, with an implicit commitment to spare as much lung parenchyma as possible. It may be this degree of variability which makes data tabulation difficult. The authors of the 2011 EOI analysis acknowledged that "Amongst the limitations is the limited information on how the recurrences were treated. However, all patients were treated in experienced sarcoma centres and it is likely that all patients received the best available treatment for their recurrence. This includes, whenever possible, complete resection of a local recurrence and/or surgical treatment of all distant recurrences in case of resectable disease."[2]

In 2006 the UK National Institute of Health and Clinical Excellence (NICE) which issues guidance to the National Health Service in England and Wales, published a manual for commissioners of cancer service on "Improving Outcomes for People with Sarcoma".[3] The manual is more about organization than practice and states that "The management of chest wall, intrathoracic sarcomas and pulmonary metastases requires a combination of skills available from a sarcoma MDT and a thoracic surgeon, often combined with plastic surgical reconstructive skills". Included in this guidance is advice on surveillance for the appearance of pulmonary metastases and states in that context "None of the 21 patients who presented between follow-up visits with symptomatic pulmonary metastases were considered candidates for potentially curative surgical resection of their metastases. Resection of pulmonary metastases was performed for 24 of the 36 patients whose asymptomatic recurrence was discovered by surveillance chest X-ray or staging CT scan"[3] based on evidence reviewed.[4,5] There is evident readiness to operate on asymptomatic pulmonary metastases in sarcoma patients but evidence for the practice, or guidance which patients are believed to benefit, cannot be inferred from this practice manual.

Thoracic surgeons are increasingly being asked to remove lung metastases as part of the overall management for a wide range of cancers. In a survey conducted by the European

Society of Thoracic Surgeons (ESTS)[6] practice varied considerably. In particular there was a wide range of opinions on the weight to be placed on factors known to be associated with survival such as the time elapsed since diagnosis of the primary tumour and the number of metastases seen on imaging. This survey was part of a wider programme of work called The European Society of Thoracic Surgeons Lung Metastasectomy Project.[7] In the introduction to the published report the leaders of the project concluded "the level of evidence to support current practice is too low to set firm recommendations to the members of ESTS." At the time of writing up The European Society of Thoracic Surgeons Lung Metastasectomy Project an up to date review of metastasectomy for sarcoma was not available and the report went to press without it. We have therefore undertaken a literature search and a systematic review of pulmonary metastasectomy for sarcoma.

Material and methods

Eligibility criteria.
A literature search was conducted according to PRISMA 2009 recommendations. [8,9] We considered eligible all the articles in the English language~~literature~~, from 1950 to the first week of June 2011, which contained at least 20 patients and any data on surgical outcome(s). Reviews and teaching articles which contributed no data for analysis were excluded. Thames Cancer Registry data were extracted for all cases of bone and soft tissue sarcoma registered from 1985 to 2008.

Types of participant
All patients of any age undergoing pulmonary metastasectomy from any type of sarcoma (bone, soft and mixed series) regardless of first time or repeated.

Type of intervention
First time or repeated metastasectomy from sarcoma.

Information sources.
A Medline search was conducted using OVIDSP interface. Medline web interface at www.pubmed.gov was also searched. The Thames Cancer Registry data was used as comparator.

Electronic Search.
The search expression used was: [lung.mp] AND [metastasectomy.mp] and [sarcoma.mp].

Study selection.
One author (MS) evaluated the reports quality from titles and abstracts identified from the electronic database searches according to the pre-defined eligibility criteria. Full text articles of studies of potentially relevant studies that met the inclusion criteria were retrieved to assess definite eligibility for inclusion.

Data collection process.

The data was extracted by 2 of the authors (MS, FF) independently and then checked by another author (TT).

Data items.
The selected papers were searched and, where available, data were extracted with respect to:

- Research methodology employed
- The purpose of the study
- The patient population from which pulmonary metastasectomy patients were drawn
- Inclusion and exclusion criteria
- Demographic data on patients selected and reported
- The interval between primary surgery and diagnosis and pulmonary metastasectomy
- Chemotherapy use
- Surgical approach, whether open or videothoracoscopic
- Surgical techniques employed
- Survival data
- Statistical analyses of factors related to outcome
- Consideration of second and subsequent metastasectomy operations
- Symptoms and respiratory performance

Thames Cancer Registry data were extracted for stage, data on interventions, sex ratio, median age and survival.

Results
The search returned 98 articles. In addition the reference lists of all papers were searched. We retrieved a further 17 articles, to make the total up to 115 having excluded duplicate records by title, authors or DOIs. Sixty five articles were excluded by title and/or abstract according to the specified criteria. The full text of the remaining 50 articles was retrieved. A further 32 were further excluded because they did not meet the initial criteria after full text review or duplicated data.

We retained 18 articles published since 1990 for inclusion in the systematic review: five report on first and subsequent pulmonary metastasectomy for bone sarcoma, [10-14] six on soft tissue sarcoma, [15-20] and four on mixed sarcoma series.[21-24] The information in Tables 1, 2, 4, and 6 are extracted from these 15 studies which include data on the patients' first pulmonary metastasectomy. Three of the 18 are confined to repeat pulmonary metastasectomy.-[25-27] One of these[27] contained 14 patients rather than the specified minimum of 20 patients but is a further report providing outcomes for repeat metastasectomy of some of the patients reported from the same institution and was therefore included.[13]

With respect to research methodology, there were no randomised controlled trials. There was one comparison study in which patients who had undergone videothoracoscopic

resection were matched with patients who had undergone a thoracotomy approach.-[24] There were no protocol based prospective studies. There was one retrospective cohort study of data obtained from a Cancer Centre's institutional Tumor Registry.[11] In other reports, cases were identified from databases which were held, as far as we could determine, at an institutional level-[10,12-17,20,23,26,27] or departmental level. [18,19,21,24,25] It appears that many of the clinical data were retrieved by retrospective case note review. A statement in a report from the M D Anderson Cancer Centre (MDACC) is probably representative of the approach to data collection: "A prospective surgical database was used to identify metastasectomy patients and missing clinical data were supplemented in a retrospective manner."[23]

In most studies the stated purpose of analysis was to report survival following first [10-21,23,24] or repeated pulmonary metastasectomy.[22,25-27] In ten of the 18 reports, statistical analyses were performed to identify patient and tumour characteristics associated with improved survival following first pulmonary metastasectomy. [11,13,14,16,18,19,21,23,25,26]

The population from which the patients having pulmonary metastases were drawn, is given in seven publications.[10-12,14,15,17,23] (Table 1) As can be seen from the footnotes to the table, no two denominators are defined in the same way and none are comprehensive at a community level. Some authors give an upper age limit (not more than 55 years,[12] 40 years,[14] or 20 years[11]) but read in context this appears to be to match the data set of operated patients rather than a prior policy. Some series include all sites while others are limited to limbs[10,12] or trunk and limbs.[11] They variously include all sarcoma patients,[23] or only those with soft tissue sarcoma.[17] The proportion of the denominator population recorded as developing pulmonary metastases ranges between 18% to 50% while the proportion of those with pulmonary metastases who have an operation to remove them varied from 5% to 88%. The report with the largest data set (MDACC) [23]) reported that only 1% of sarcoma patients have a pulmonary metastasectomy. We have not found it possible to determine how much of the variation in the recorded data is attributable to varying selection in clinical practice, the different biology of tumours according to histology, tumour site, or variation amongst patients. A large amount of the variation appears to depend on how wide the net is cast in capturing the denominator.

Amongst these 18 studies of pulmonary metastasectomy for sarcoma the inclusion criteria are much as those proposed by Thomford [28] that the cancer at the primary site was eradicated, controlled, or amenable to control;[10,12,13,15,17-22,24,26,27] that the metastatic lung disease was amenable to complete resection;[10,11,13,15,18-21,24,26,27] that there was no metastatic disease elsewhere;[10,12,13,15,17-22,24,26,27] and that the patient was expected to withstand the loss of lung tissue necessary to give clearance.[10-12,15,17-22,24,26,27] In individual instances authors specified that there should be no mediastinal or chest wall involvement;[17] absence of pericardial or pleural effusions;[12] that the overall operative risk was acceptable;[26] or that there was no other available more effective treatment.[19] In one report, increased size on chemotherapy was allowable, but not an increase in the number of metastases.[24] One

study with five subgroups gave group by group criteria which, read in context, appeared to defined after exploration of the available data to facilitate analysis and reporting.[23] Criteria for inclusion or exclusion in the metastasectomy cohort were not found in three studies.[14,16,25]

Data are given in Table 2 for the 15 studies which include data on the first pulmonary metastasectomy, for a total of 1168 patients. The average age of bone sarcoma patients was 17 years based on 377 patients in four studies with calculable data [10,12,13], excluding the reports limited to patients aged <21 years[11] or <40 years.[14] For soft tissue sarcoma the average age was 46 based on five studies including 277 patients[16-20] excluding a study where median and range were given.[15]

Male sex was predominant in bone sarcoma (65% of 532 patients) but not in soft tissue sarcoma reports (50% of 277 patients). These differences in age and sex preclude meaningful amalgamation of outcome data following pulmonary metastasectomy for bone and soft tissue sarcoma.

The interval between resection of the primary and first pulmonary metastasectomy was provided in 9/15 reports and was highly variable as can be seen from Table 2. There is a degree of consistency in the median interval of 1-2 years but half of the authors providing data, operated on synchronous metastases (5 of 10). Repeat metastasectomy was performed in 43% of patients based on 14/18 reports in which the data could be extracted. (Table 3)

Chemotherapy was frequently used but schedules were variable both within and between publications. Some authors stated that preoperative and/or post operative chemotherapy was given routinely in all cases[10,21,26,27] but more often the practice varied. [11-14,16,18,21] One paper states "The only constant was that when the disease-free interval was <2 years with a single lung metastasis, no chemotherapy was added to surgery" and another that it was at the discretion of the oncologist.[19] One group used chemotherapy preoperatively only when there were six or more metastases.[17] It was also implicit in the text of several papers that response to chemotherapy was part of the clinical evidence used to help select patients for surgery; non responding and progressing patients were less likely to be selected for pulmonary metastasectomy and this information is not necessarily explicit in the report. This statement in the report from the MDACC is representative of this approach: "Those who developed metastatic disease early with multiple pulmonary nodules were treated initially with chemotherapy to determine the pace of disease progression, if any, on treatment. Patients responding to chemotherapy, those with stable disease, and those with slow progression were referred for resection while those with rapidly progressive metastatic disease received alternative chemotherapy treatment."[23]

Whether videoscopic or open surgery was used, and if open through what incision, and the surgical technique used to resect the metastases, are summarised in Table 4 for 12/15 papers including data on first metastasectomy operations.[10-13,16-21,24] The remaining three of the 15 studies were not explicit with respect to the surgical approach.

In the more common surgery for carcinoma metastasised to the lung, lymphadenectomy has become an important consideration.[29] In these reports concerning sarcoma patients, hilar nodes were not routinely dissected[19] or maybe dissected "when necessary".[12] This avoidance of lymphatic resection appears to be linked to the lower rate of lymphatic spread in sarcoma compared with other thoracic malignancy in which further spread from the metastases to mediastinal lymph nodes is frequent.[29]

There is a strong evident preference for open surgery (96% of patients had a thoracotomy of some form) with considerable emphasis placed by several authors on the importance of manual palpation of the lung[10-12,16,17,20,22] which cannot be achieved through a purely videoscopic approach. One study specifically addressed the question for whether the less invasive thoracoscopic approach might be as effective[24] and it was concluded that it might be an option if there are no more than two metastases but this was not derived from data analysis presented in the publication. The general use of thoracotomy, often bilateral, and repeated metastasectomy in 43% of patients overall represents a high treatment burden for patients. (Table 3)

Thames Cancer Registry data for sarcoma were studied to provide some context to the overall survival rates of patients with sarcoma. (Fig.1) The Registry has employed its own 4-level staging system since 1960 and stages around 60% of all solid tumours. The classification system uses information in the patients' notes to determine if the disease is local (stage 1), has extension beyond the organ of origin (stage 2), has regional lymph node involvement (stage 3) or has metastasised (stage 4). Survival data by stage for two complete decades 1985-1994 and 1995-2004 for both bone and soft tissue sarcoma are provided in Fig.1. For patients entered as Stage 4 bone sarcoma (metastatic disease at the time of registration) in those two decades five year survival of 20% and 25% are recorded for bone sarcoma and 13% and 15% for soft tissue sarcoma.

The Registry does not include full data on treatment but does provide data on the highest surgery code. These are presented in an abbreviated form in Table 5. According to the selection criteria set out above, since the stated first criterion for pulmonary metastasectomy was that a radical operation had been successful at the primary cancer site, it is amongst the 8% of bone sarcoma patients and 21% of soft tissue sarcoma patients that pulmonary metastasectomy patients would be found.

Five year survival data are plotted against publication date (Fig.2) and the size of the series (Fig.3) for 14 of these 15 studies where the data are given, to allow for this visual inspection of time or case volume. Three and/or five years survival for the 15 studies including first (and subsequent) metastasectomy data are plotted in Fig.4

Five year survival data are set out in Table 6 sorted by tumour type from 14 of the 15 studies including first (and subsequent) metastasectomy data. Together these provide data on 1196 patients having metastasectomy from as early as 1976 [16] to as recently as 2008.[14] Overall about a third of patients who have had pulmonary metastasectomy for

bone sarcoma and about a quarter who have had pulmonary metastasectomy for STS survive beyond five years. Survival data for two complete decades 1985-1994 and 1995-2004 are included in the table to provide a reference measure of survival in all sarcoma patients in the registry who were classified as Stage 4, that is sarcoma metastasized at presentation/registration. Direct comparison cannot be made but it is a reminder that an implicit assumption that the five year survivals of the patients in the pulmonary metastasectomy series would have approached zero would be incorrect. Summary data of sex distribution and the median age for patients in two completed decades (1985-94 and 1995-2004) with bone and soft tissue sarcoma in Table 7.

We can reasonably deduce

1. that five year survival after pulmonary metastasectomy is not necessarily attributable to the metastasectomy
2. that five year survival does not equate to cure since there are five year survivors with metastatic disease.

Data are not available in the publications concerning the fate of patients beyond five years and there are no narrative accounts of the clinical course of these patients. However a number of the authors include, in their narrative, a statement of belief in cure for patients who have recurred in the lung or that their surgery has curative intent[12,14,16,17,19,24,25] and the phrase "potentially curative resection" is included in NICE guidance.[3] Illustrative statements from recent publications are these from 2009 and 2010:

"Given the lack of effective systemic therapies, PM remains the only potentially curative treatment for STS lung metastases as long as all known disease can be completely resected with negative margins."[16]

"We demonstrate that after repeated metastasectomies, a subset of patients can be cured."[14]

Other author explicitly exclude likelihood of cure attributable to pulmonary metastasectomy. Antunes writes "The 5-year survival may reach 50%, although true cure is extremely rare, the majority of patients eventually dying of the disease."[10] And Sardenberg and colleagues state "It should be emphasized that surgery does not change the biology of the tumor or the metastatic process, and a definitive cure for most patients represents the combination of host histology, tumor spread, response to systemic therapy, and surgical resection, which together render the patient free of disease."[19]

Several reports include multivariate analysis to seek factors that might determine a greater or lesser survival rate. The interval between diagnosis or resection of the primary cancer and the metastasectomy surgery is the commonest factor reported as being significant [11,18,19,21,23,25,26] survival usually being better if the interval was 12 months or longer. Fewer metastases was also associated with better survival [13,14,18,19,23,25,26,30] most commonly at a number of about three or fewer. Female

sex [14,16] was also favourable. Patients in whom there was substantial necrosis following chemotherapy survived longer.[10,11,14,22]

No data were found regarding respiratory function or symptoms in any of the 18 reports. Where mention was made of respiratory function in the text it was related the decision to operate. Several authors explained that a point had been, or might be reached, where respiratory function or respiratory reserve precluded further metastasectomy. No measurement of this or its consequences for the patients was provided in any report.

Discussion

A major limitation, when interpreting reports of pulmonary metastasectomy for sarcoma, is the absence of control data. It is usual in surgery to rely heavily on evidence from case series, either in the form of retrospective case note reviews or less commonly prospective cohort studies. When there is a clear temporal and mechanistic relationship between cause and effect, and the signal is evident from the noise, observational studies often provide sufficient evidence.[31] The simple evidence of cause and affect cannot be invoked where there is a widely variable time course and multimodal treatments as is the case in protracted, repeated and multimodal treatment of sarcoma.

Efficacy, effectiveness, and cost effectiveness are different measures of the benefits of a treatment. Pulmonary metastasectomy has been shown to be efficacious in that complete macroscopic clearance has been achieved; in appropriately selected cases, R0 resection of all known pulmonary metastases can be consistently accomplished. Whether pulmonary metastasectomy is effective in prolonging life requires proof that survival has been extended, by metastasectomy, beyond that which would have occurred without pulmonary metastasectomy. Cost effectiveness requires, in addition to survival, measures of health gained, measures of health lost due to death and complications, and for these to be costed in comparison with any alternatives, including no treatment. This third measure, estimation of cost effectiveness is outside the scope of this review and depends on first establishing effectiveness.

Evaluation of the effectiveness in preventing or postponing death by pulmonary metastasectomy is the common objective in these clinical reports. The existing practice is believed to be effective based on repeated experience world wide for over forty years. In 1971 thoracic surgeons at Memorial Sloane Kettering reported on 22 patients with treated osteogenic sarcoma in whom they performed lung resections. [32] The meticulous case by case communication of that experience merits revisiting. (Fig.2)

In the discussion that followed Beattie modestly states:
"We reported these data with some reluctance, since they really constitute a progress report on a clinical research project underway at Memorial Hospital. We used osteogenic sarcomas because they are such serious tumors. There are occasional spontaneous regressions and good results; but you saw in the figures Dr. Martini showed that with amputation we have had a 17% five-year cure rate. Of the 83% of patients who died, 5% lived three years. Very occasionally a patient would go on longer before dying."[32]

Twenty-years later [33] Beattie reported further:
"Twenty-year follow-up reveals that at least four of the six survivors at 10 years survived more than 19 years; one was lost to follow-up. The patient who died of metastatic osteogenic sarcoma more than 19 years after her first thoracotomy had a total of nine thoracotomies."

An implicit assumption is embedded in many subsequent reports that none of these patients would have lived beyond five years without metastasectomy. There are other reasons, apart from having had pulmonary metastasectomy, for patients with pulmonary metastatic disease to be alive at and beyond five years. These patients are carefully selected and although it is not possible to put a reliable figure on it, they are a minority of all patients with the disease.[2] (Table 1) It is appropriate to select patients for surgery and yet comments such as– "survival of (surgically treated) patients was significantly better than of patients ineligible for metastasectomy. P<0.00001"[14] is not an appropriate or meaningful statistical comparison: the difference is evident but how much is due to the selection and how much to the surgery, cannot be determined.

The identifiable factors for selection of suitable patients include fewer metastases and a longer interval between the diagnosis and treatment of the primary and the resection of pulmonary metastases.[34,35] Others which appear in some analyses are tumour doubling time and the size of the nodule(s) which under surveillance is a proxy for rate of growth. These are prognostic features for survival under any circumstance. We also know from the Thames Cancer Registry data that there are 20-25% of patients with osteosarcoma and about 15% with soft tissues sarcoma, with metastases at the time of registration, who are alive beyond five years. (Table 6) The narrative accounts record that there are some natural long term survivors: "one patient not operated on remains alive 18 years after not having surgery."[14] "Long-term survivors appear to belong to a subset of patients with indolent, lung-only disease."[36] These natural survivors, who are likely to have slower progression, and fewer metastases, are likely to be disproportionately frequent amongst patients selected for metastasectomy [37] as seen in the graphical depiction, for the selection process is not random. (Fig.6). More than thirty years ago Aberg first proposed that selection might be the major factor determining survival after pulmonary metastasectomy [38] and returned to this question in 1997. [39] It is of note that none of the authors cite Aberg. It is known that "citation distortions create unfounded authority" [40] and citation network analysis.[41]

In fact the effect of selection may easily be underestimated. Multivariable analysis cannot detect more than a limited number of factors in these relatively small series. All of these factors may exhibit covariance and they are all indices of the relative aggressiveness of a cancer. Failure for one or more of these factors to reach significance in any particular Cox model does not refute the overall finding. Furthermore, if the knowledge of previous finding leads to the exclusion of some patients, the range of that variable is reduced and it is less likely to be found in subsequent analyses. [42]

In this group of young and therefore physically resilient patients there seems to be a strong desire to never say no, and to push the boundaries for selection for metastasectomy. It is well established that patients with more metastases are unlikely to live long after metastasectomy. Nevertheless there is no apparent upper limit in many of the reports nor was there for 85% of surgeons in the ESTS survey.[6] Amongst the reports pulmonary metastasectomy in the present systematic review some surgeons report very high numbers of metastases resected. For example "The authors have removed as many as 80 to 100 nodules during a single thoracotomy" [22] and in the COSS report "The highest number of pulmonary nodules surgically removed was 250"[1] are out of line with the observational evidence that above a count of relatively few metastases, outcomes are too poor to justify this surgery. Maybe these high numbers reflect the observation that the preoperative count of nodules underestimates the true extent of the disease "It is interesting that despite the presence of only three or four nodules on many CT scans, up to 50 or more nodules were found and removed in a number of these patients."[22] The issue of the relative reliability of modern imaging versus surgeons' palpation of the lung has been considered elsewhere with varying conclusions.

The extent of necrosis caused by chemotherapy evident in the excised nodule was found to be a favourable feature for survival.[10] The clinical response or failure to respond to chemotherapy was given as factor in selection in several series. Both of these observations are evidence that chemotherapy is having an effective in these patients and has had a demonstrable effect on their disease. Why then should a survival difference be attributed to the surgery?

There is a firm belief that if sarcoma recurs in the lungs, and the patient is still within the criteria for resection, further resections should be performed. "The authors concluded that patients persistently free of the primary osteosarcoma who developed recurrent resectable metastatic disease of the lung should be considered for reoperation a second, third, or fourth time, as these patients had similar DFI curves after five-years."[26] This belief is supported by what might be inappropriate data interpretation. Consider these statements for example: "Prognostic factors for increased survival included 3 or greater redo pulmonary operations"[23]; "patients with complete resection for recurrent pulmonary metastasis show a significantly better prognosis after repeat pulmonary metastasectomy"[27] and "repeat metastasectomy for recurrent pulmonary metastasis also provided a favorable overall survival (P <0.041)".[20] To undergo a second metastasectomy a patient has to have survived, and been without evidence of disease for a reasonable length of time, to meet the criteria for each subsequent operation. The problem is exemplified by Sardenberg and colleagues. Survival was measured from the first thoracotomy for pulmonary metastasectomy (confirmed with the first author) and was 15 months, 45 months and 48 months, in 35 patients having only one surgical episode, 24 who had two and 13 who had three. The authors provide a statistical analysis (P=0.077) of the association between more thoracotomies and longer survival. They neglect the fact in their interpretation that survival after surgery, and for a reasonable period of time, was a requirement to move to the next analytical group.[19] This way of presenting the data maximizes survivor bias: ongoing survival is an entry criterion to having a further metastasectomy operation.

We found no of data, or even a narrative account, concerning the effect of surgery on symptoms. The patients who are regarded as candidates for metastasectomy are generally detected on surveillance and presentation with symptoms probably distinguishes patients as being not suitable for metastasectomy, either because it represents extrapulmonary disease of the pulmonary disease is too advanced. The evidence cited in NICE guidance[3] is as follows: "Detection on the basis of symptoms occurred in 21 patients. Fifteen of these patients presented between scheduled visits. Seven patients were symptomatic primarily on the basis of their metastatic pulmonary disease. These patients had diffuse metastatic disease in all cases, with documented synchronous recurrence outside the lung, and none was resectable."[5] What is implicit in many of the reports reviewed is that ultimately they call a halt to repeated thoractomies because the patient respiratory function will not withstand further surgery and loss of lung tissue.

Two publications[45,46] which appeared in 2011 after completion of our review and data analysis, and following submission, have been brought to our attention. They come from prominent North American institutions and appeared in a specialist thoracic surgical journal Annals of Thoracic surgery. The report from Brigham and Women's Hospital, Boston, Massachusetts states in its title "Repeated and aggressive pulmonary resections for leiomyoma metastases extends survival". The report is of 82 patients with a variety of bone and soft tissues sarcomas between 1989-2004. Repeat metastasectomy was performed in 28/82 with some patients having 3, 4 or 5 thoracic operations. Operated patients with leiomyosarcoma 31/82 had a median survival of 70 months compared with 24 months for other sarcoma subtypes. No control data for survival amongst comparable patients not operated upon are provided. The text confirms that the surgery was repeated and aggressive but that survival was extended as a result cannot be inferred from the data presented for the reasons given already. The report from Massachusetts General Hospital is of 97 patients with 13 sarcoma subtypes operated on for pulmonary metastases between 2002 and 2008.[46] They report that of 69% of 29 patients who had multiple operations were alive at five years compared with 41% of 60 patients who had a single operation and find the difference to be statistically significant and the bottom line of the conclusions reads "Repeated pulmonary metastasectomy in select patients may improve survival despite recurrent disease." But patients have first to be survivors to be candidates for surgery, a point the authors make themselves in their discussion "Patients in whom disease rapidly recurred after surgery (either as a local recurrence or disseminated disease) were probably selected out from repeated surgical resection."[46] Neither of these papers provides evidence on symptomatic benefit for these patients.

While there are some long term survivors amongst those who have this surgery the absence of control data leaves Aberg's challenge[38,39] unrefuted. His hypothesis was that patients ~~The possibility remains that practice is to select for surgery those who were~~ destined to survive longer are more likely to be selected for surgery and it is the process of selection, rather than the effect of pulmonary metastasectomy, that is responsible for any survival difference perceived. ~~and to reviews presented attribute the longer survival inherent in the selected patients to the pulmonary surgery rather than to the selection for that surgery.~~ Although it would be challenging to perform, a randomised controlled trial

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may be necessary if we are to see the signal from the noise in this area of clinical practice.

Legends to figures

Figure 1
Thames Cancer Registry data. Kaplan Meier survival plots by stage for decades 1985-1994 (above) and 1995-2004 (below) for bone (left) and soft tissue sarcoma (right). Stage 4 (that is metastasised at the time of diagnosis/registration) in red.

Figures 2
Five year survival rates plotted against the publication date.

Figure 3
Five year survival rates plotted against the size of the series.

Figure 4
Three and five year survival rates from publications in Table 6. (Bone sarcoma red, soft tissue sarcoma green and mixed series blue.)

Figure 5
The full display of essential features of the patients and their with survival from primary resection to metastasectomy and subsequently. From Martini et al 1971

Figure 6
A conservative estimate of natural five year survivors is set at 5% (15/300 in this depiction) and they are in green. Ranking patients on the Y and X axes from least to most favourable based on fewer metastases and longer interval since diagnosis might have the effect of clustering these natural survivors as shown. If selection for surgery is also based on these factors, it might be the selection rather than the surgery which is associated with a higher than anticipated survival rate shown here as 10/25 or 40%.

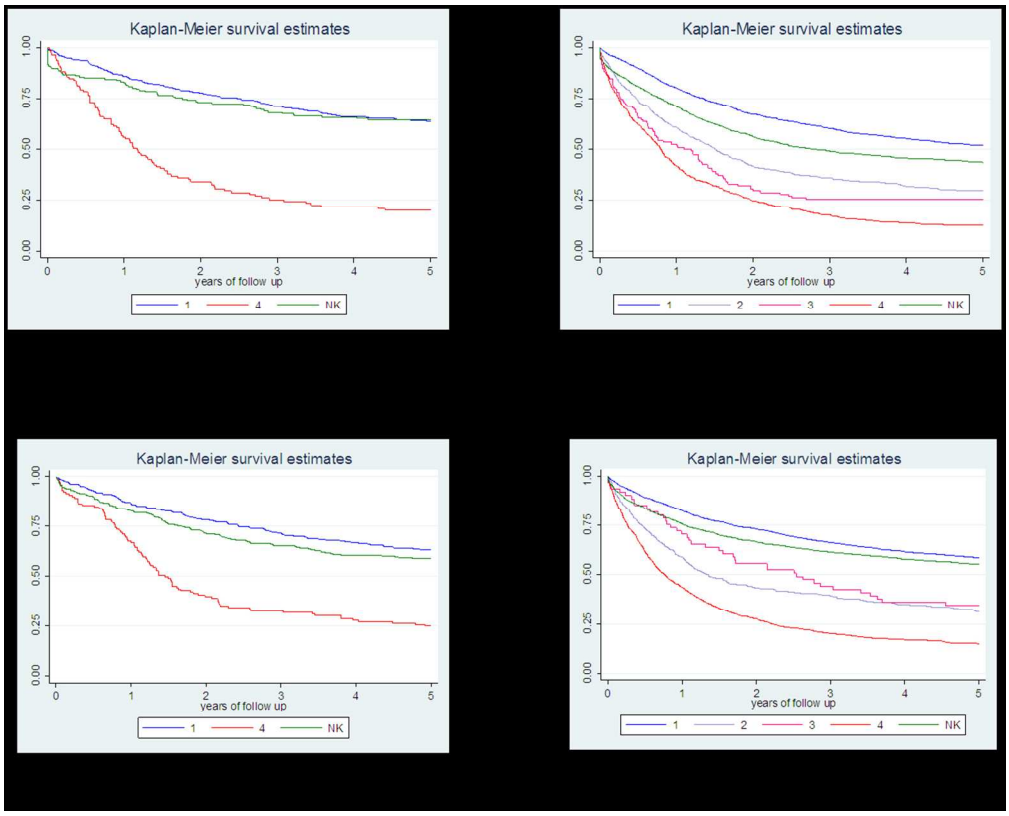
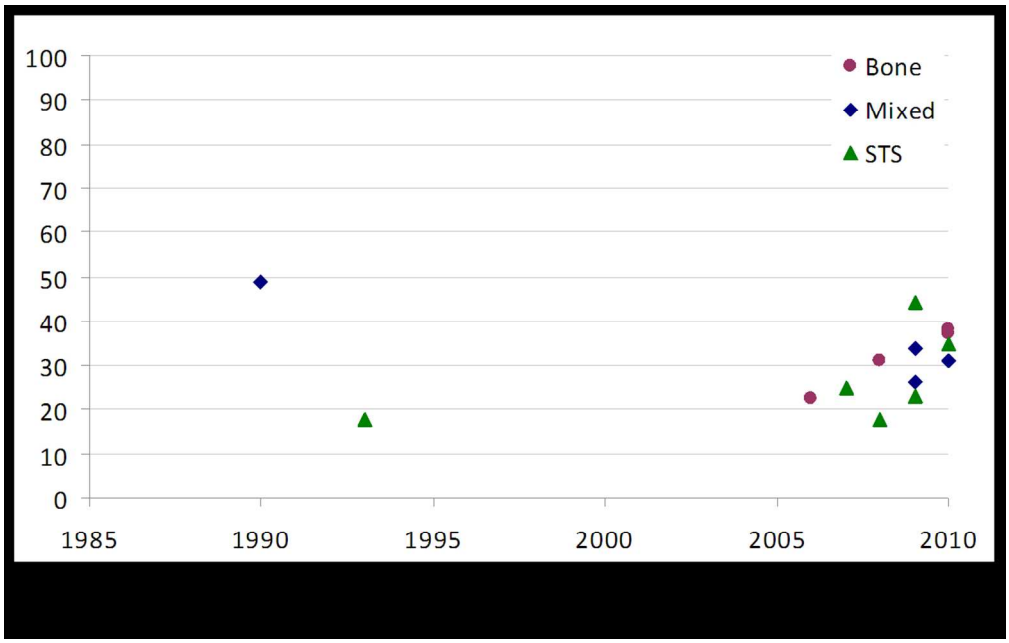


Figure 1
Thames Cancer Registry data. Kaplan Meier survival plots by stage for decades 1985-1994 (above) and 1995-2004 (below) for bone (left) and soft tissue sarcoma (right). Stage 4 (that is metastasised at the time of diagnosis/registration) in red.

214x172mm (150 x 150 DPI)



Figures 2
Five year survival rates plotted against the publication date.

228x144mm (150 x 150 DPI)

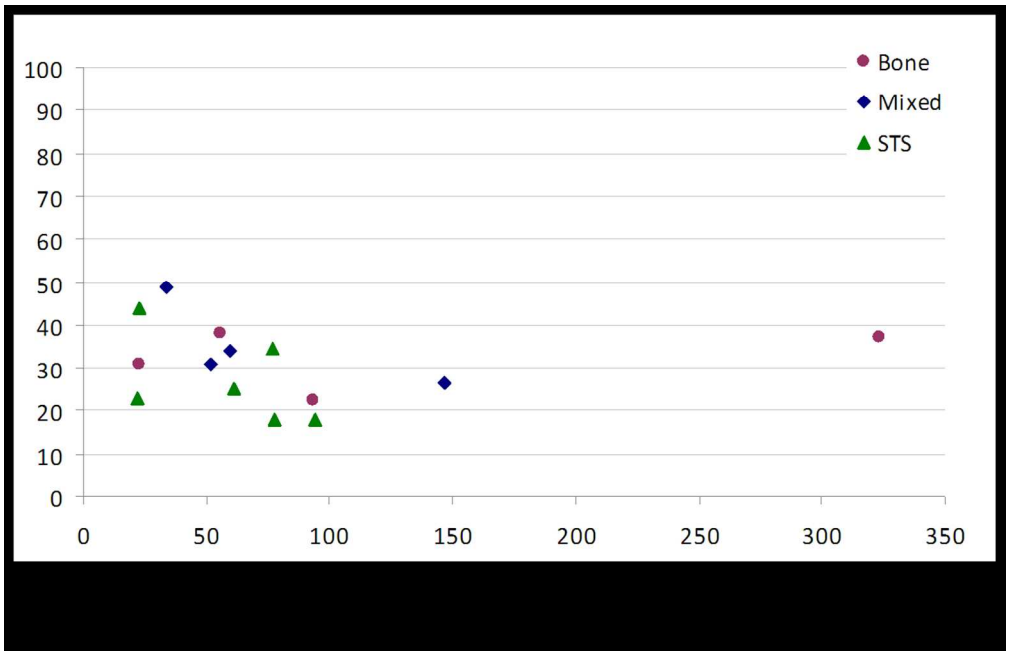


Figure 3
Five year survival rates plotted against the size of the series.

224x144mm (150 x 150 DPI)

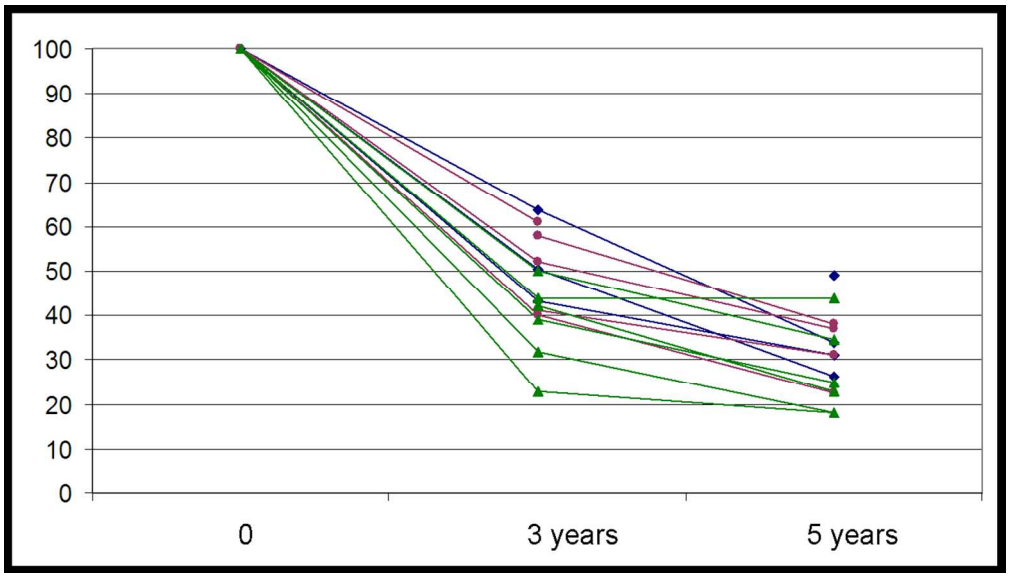


Figure 4
Three and five year survival rates from publications in Table 6. (Bone sarcoma red, soft tissue sarcoma green and mixed series blue.)

226x127mm (150 x 150 DPI)

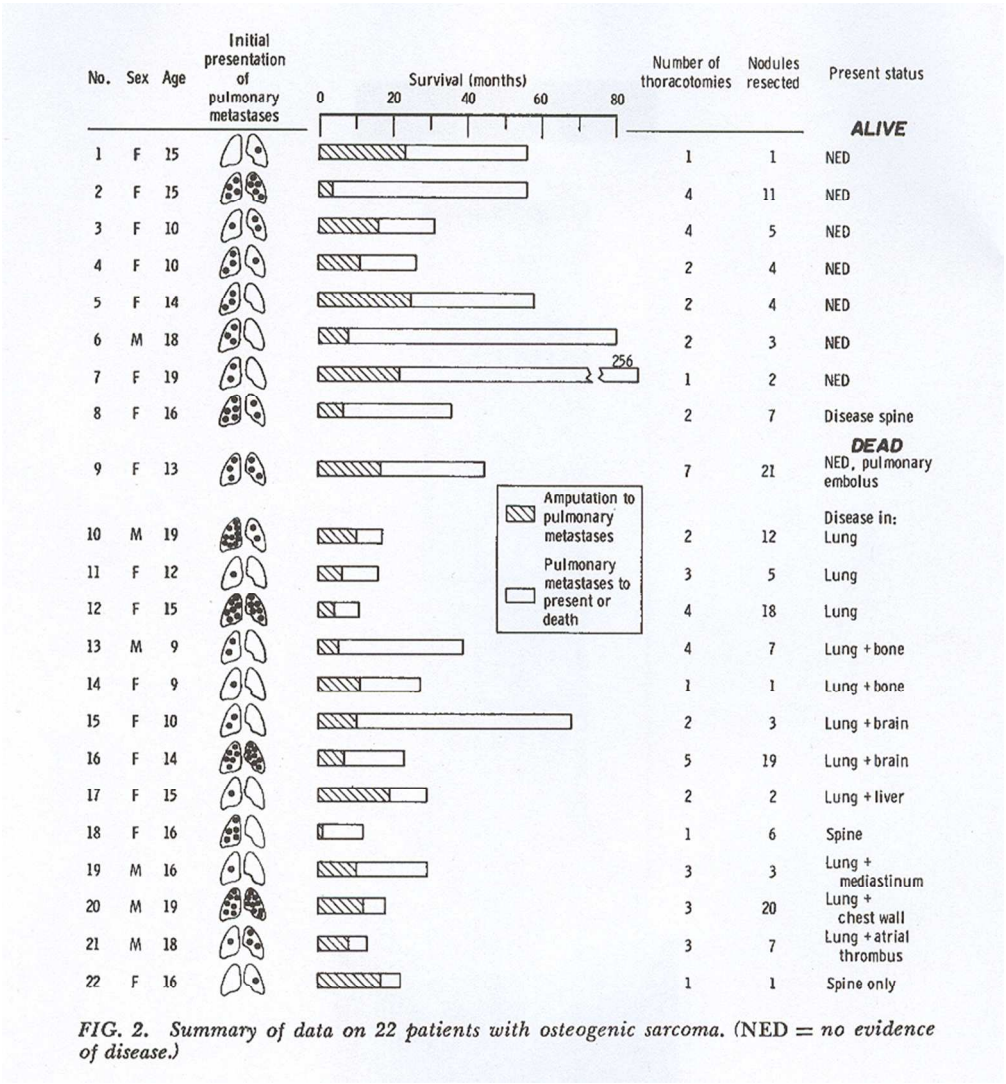


FIG. 2. Summary of data on 22 patients with osteogenic sarcoma. (NED = *no evidence of disease.*)

Figure 5
The full display of essential features of the patients and their with survival from primary resection to metastasectomy and subsequently. From Martini et al 1971

150x161mm (150 x 150 DPI)

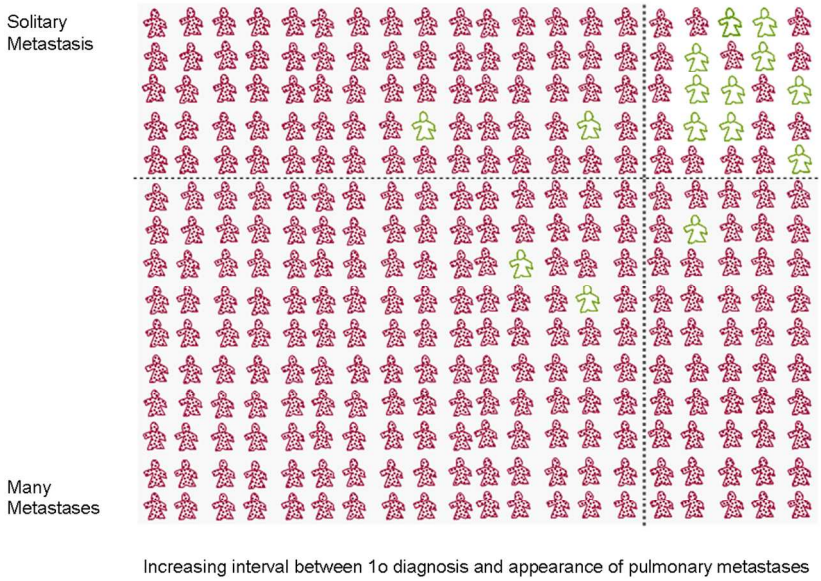


Figure 6
A conservative estimate of natural five year survivors is set at 5% (15/300 in this depiction) and they are in green. Ranking patients on the Y and X axes from least to most favourable based on fewer metastases and longer interval since diagnosis might have the effect of clustering these natural survivors as shown. If selection for surgery is also based on these factors, it might be the selection rather than the surgery which is associated with a higher than anticipated survival rate shown here as 10/25 or 40%.

235x176mm (150 x 150 DPI)

Publication	Histo	Start Date	End Date	All registered sarcoma patients A	Patients with pulmonary metastases B	Pulmonary Metastasectomy as reported in cited papers in systematic review C	Proportion of sarcoma patients with pulmonary metastases (=B/A)	Proportion of Patients with pulmonary metastases who have metastasectomy (data as in reports) (=C/B)	Proportion of all sarcoma patients who have pulmonary metastectomy (=C/A)
Antunes 1999	Bone	1989	1997	198[a]		31			16%
Harting 2006	Bone	1980	2000	272[b]	137[c]	99	50%	72%	36%
Briccoli 2010	Bone	1985	2005	1197[d]	369[e]	323	31%	88%	27%
Buddingh 2009	Bone	1990	2008	197[f]	88[g]	56	45%	64%	28%
Gadd 1993	STS	1983	1990	716[h]	135[i]	78	19%	58%	11%
Rehders 2007	STS	1991	2002	678[j]	121[k]	61	18%	50%	9%
Blackmon 2009	Mixed	1998	2006	15744[l]	4355[m]	234	28%	5%	1%

Table 1 Data from reports providing the number of patients from which the study population was derived

[a]patients operated on for osteogenic sarcomas of the limbs were followed in their centre
[b]patients with osteosarcoma of the trunk or extremities who were younger than 21 years and who had medical records available for review
[c]developed or presented with radiographically evident pulmonary nodules. These 137 patients formed the initial study cohort.
[d]patients with histologically proven HGOS of the extremity 55 years old or younger diagnosed at their Institution
[e]first recurrence with metastases located only in the lung
[f]patients under the age of 40 treated for high-grade OS at the Leiden University Medical Center
[g]patients who had pulmonary metastases either at diagnosis or during follow-up
[h]adult patients with a primary or locally recurrent extremity soft tissue sarcoma admitted to MSKCC
[i]patients with pulmonary metastases
[j]patients with STS were treated at the Department of Surgery, University Hospital
[k]pulmonary metastasis of STS occurred during follow-up,
[l]patients with soft tissue and bone sarcoma referred to The University of Texas M.D. Anderson Cancer Center
[m]patients diagnosed with sarcomatous pulmonary metastases

Author	Sarcoma patients who have pulmonary metastasectomy (N)	Age mean (years)	Age range (years)	Sex Males	Sex %male	Median interval between primary and metastases (months)	Range (months)	Mean number of mets resected	Range
Bone									
Antunes 1999	31	25	10-54	21	68%	22	4-122	3.2	1-8
Harting 2006	99	13.9	+/- 4.2	67	68%	0 in 17%	0-NF		1->10
Briccoli 2010	323	16	4-55	201	62%	NF		NF	NF
Chen 2008	23	19	6-68	15	65%	19	0-108	5.0	
Buddingh 2010	56	NF	NF	40	71%	NF			
Soft Tissue									
Gadd 1993	78	(55)*	17-85	NF		14	1-152	NF	NF
Smith 2009	94	49	9-75	47	50%	15	0-NF	2.5	1-105
Rehders 2007	61	42	18-47	33	54%	21	0-3	5.0	1-48
Garcia Franco 2009	22	41	13-82	10	45%	18	5-84		
Sardenberg 2010	77	45	NF	37	48%	NF		3.5	
Chen 2009	23	53	15-86	12	52%	NF	0-168		
Mixed									
Snyder 1991	34	23	NF	20	59%	19	<6->24	11	NF
Blackmon 2009	234	<50*		123	53%	Varied	NF	NF	NF
Gossot 2009	60	40		34	57%	18	NF	NF	NF
Garcia franco 2010	52	20	5-74	31	60%	20	5-189	NF	NF

Table 2 Summary data on 15 papers reporting on series of patient undergoing a first pulmonary metastasectomy operation for sarcoma.
* median age
NF means data were not found

Series	N 1st	N 2nd	Multiple
Rehders 2007	61	13	21%
Antunes 1999	31	8	26%
Garcia franco 2010	52	16	31%
Garcia Franco 2009	22	7	32%
Chen (EJSO) 2009	23	8	35%
Smith 2009	94	33	35%
Briccoli 2005	267	94	35%
Briccoli 2010	323	122	38%
Buddingh 2010	56	26	46%
Sardenberg 2010	77	37	48%
Gossot 2009	60	33	55%
Blackmon 2009	234	141	60%
Chen (EJCTS) 2008	23	14	61%
Snyder 1991	34	28	82%

Table 3. The proportion of patients who have second or subsequent metastasectomy. This does not include staged bilateral thoracotomies which are regarded as a single intervention. Reports are ranked according to the proportion having second and subsequent metastasectomy interventions. Sequential staged operations (for example lateral thoracotomies planned with an interval of 1-3 weeks) are considered by the authors as a single episode of treatment.

Report	Surgical approach	Surgical technique
Snyder 1991	Thoractomy Bilateral disease staged thoracotomy, 1-2 weeks interval 16/34	Enucleation
Antunes 1999	Thoracotomy 30/31 Median sternotomy 1/31	Enucleation Wedge resection Lobectomy
Harting 2006	Thoracotomy, Staged or simultaneous bilateral thoracotomies Median sternotomy	
Briccoli 2010	Thoracotomy Bilateral thoracotomies	Wedge resection Lobectomy Pneumonectomy
Garcia Franco 2010	Thoracotomy 30/52 Sequential bilateral thoracotomy 7/52 VATS) 10/52 Clamshell 5/52	Wedge 44/52 Lobectomy 6/52 Exploratory thoracotomies 2/52[i]
Chen 2008	Thoracotomy	Wedge 22/23 Lobe 1/23
Smith 2009		Wedge 74/94 Lobectomy 17/94 Pneumonectomy 3/94 Resection of other thoracic disease 16/94
Rehders 2007	Thoracotomy 29 (48) Bilateral thoracotomy, 2 sessions 10 (16)[ii] Median sternotomy 22 (36)	Wedge resection 52 (85) Lobectomy 9 (15)
Garcia Franco 2009	Thoracotomy 19 VATS 2 Sternotomy 1	Wedge 19 Lobectomy 3
Sardenberg 2010	Thoracotomy Staged bilateral thoracotomy	Complete resection with 10mm margin
Chen EJSO 2009		Wedge resection 21/23 Lobectomy 1/23 Pneumonectomy 1/23
Gossott 2009	Thoracotomy 29 VATS 31 In a comparative study of the two approaches	

Table 4 Surgical approaches and resection techniques in reports of 1st time pulmonary metastasectomy

[i] That is to say no resection of sarcoma was performed in these patients.
[ii] These patients have planned sequential operations about two weeks apart and it is regarded as a single intervention as opposed to a repeat metastasectomy operation.

	Bone		STS	
	N	%	N	%
Total removal of organ, or operation stated to be radical	145	8%	3203	21%
Partial or debulking operations on the primary tumour	648	35%	4935	32%
Lymphadenectomy	2	0.1%	171	1%
Non-tumour removing surgical treatment	160	9%	245	2%
Haematological procedure (e.g. bone marrow transplant)	2	0.1%	19	0.1%
Investigative procedure only	298	16%	2072	14%
Type of surgery not known	11	1%	59	0.4%
No surgery recorded	581	31%	4559	30%
	1847	100%	15263	100%

Table 5 Highest Surgery Code of Thames Cancer Registry sarcoma patients 1985-2008

Author	Sarcoma patients who have pulmonary metastasectomy (N)	Five year survival where provided	Middle date of metastasectomy series and date ranges for TCR
Bone			
Harting 2006	93	23%	1991
Briccoli 2010	323	37%	1996
Chen (EJCTS) 2008	23	31%	1999
Buddingh 2010	56	38%	2000
TCR		20%	1985-1994
TCR		25%	1995-2004
Soft Tissue			
Gadd 1993	78	18%	1987
Smith 2009	94	18%	1989
Rehders 2007	61	25%	1997
Sardenberg 2010	77	35%	1999
Chen (EJSO) 2009	23	44%	1999
Garcia Franco 2009	22	23%	2002
TCR		13%	1985-1994
TCR		15%	1995-2004
Mixed			
Snyder 1991	34	49%	1984
Garcia franco 2010	52	31%	2002
Blackmon 2009	234	26%	2003
Gossot 2009	60	34%	2004

Table 6 Five years survival and Thames Cancer Registry summary data

Five year survival from 14 of the 15 studies reporting first (and subsequent) pulmonary metastasectomy operations. They are grouped by sarcoma type and then by mid year of the series to aid visual inspection for time trends. Thames Cancer Registry (TCR) five year survival data for Stage 4 patients are provided for two complete decades of data overlapping the reported series. These TCR patients all had metastases at presentation but not necessarily lung or lung only.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5*6-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19/28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Year	Cases	M/F ratio	Median age
Bone			
1985-1994	762	1.31	35
1995-2004	709	1.35	33
Soft tissue			
1985-1994	5615	0.98	56
1995-2004	6256	0.82	58

Figure 7

Sex ratio and median age of patients in Thames Cancer Registry for whom survival data are provided in Table 6.

Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data

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Manuscript ID:	bmjopen-2012-001736.R1
Article Type:	Research
Date Submitted by the Author:	31-Jul-2012
Complete List of Authors:	Treasure, Tom; UCL, Clinical Operational Research Unit Fiorentino, Francesca; Imperial College, National Heart and Lung Institute (NHLI) Cardiothoracic Surgery Scarci, Marco; Papworth Hospital, Cardiothoracic Surgery Moller, Henrik; Kings College London, Thames Cancer Registry Utley, Martin; UCL, Clinical Operational Research Unit
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Evidence based practice, Surgery
Keywords:	Sarcoma < ONCOLOGY, Cardiothoracic surgery < SURGERY, Adult thoracic medicine < THORACIC MEDICINE

Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data

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All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

There was no funding for this study

Contributorship statement

- Tom Treasure instigated the study, reviewed and revised data extraction, created the data tables, did a critical textual review, wrote the first draft and edited all subsequent drafts.
- Francesca Fiorentino did the initial data extraction and created the final versions of the figures.
- Marco Scarci did the initial literature search and subsequent updated literature searches.
- Henrik Moller was responsible for identification, extraction and analysis of comparative data from the Thames Cancer Registry.
- Martin Utley oversaw data analysis, interpretation and presentation.
- All authors reviewed the manuscript at each stage and have approved the submitted version.

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At Thames Cancer Register we thank Marie Horton and Alexander Massey for data analysis.

We are willing to share data.

ABSTRACT

Objectives: Sarcoma has a predilection to metastasis to the lungs. Surgical excision of these metastases (pulmonary metastasectomy) when possible has become standard practice. We reviewed the published selection and outcome data.

Design: Systematic review of published reports that include survival rates or any other outcome data. Survival data were compared with those in a cancer registry.

Setting: Specialist thoracic surgical centres reporting the selection and outcome for pulmonary metastasectomy in 18 follow up studies published 1991-2010.

Participants: Patients having one or more of 1357 pulmonary metastasectomy operations performed between 1980 and 2006.

Interventions: All patients had surgical pulmonary metastasectomy. A first operation was reported in 1196 patients. 43% of 1357 patients had subsequent metastasectomy, some having 10 or more thoracotomies. Three studies were confined to patients having repeated pulmonary metastasectomy.

Primary and secondary outcome measures: Survival data to various time points usually five years and sometimes three or ten years. No symptomatic or quality of life data were reported.

Results: 34% and 25% of patients were alive five years after a first metastasectomy operation for bone or soft tissues sarcoma. Better survival was reported with fewer metastases and longer intervals between diagnosis and the appearance of metastases. In the Thames Cancer Registry for 1985-1994 and 1995 to 2004 five year survival rates for all patients with metastatic sarcoma were 20% and 25% for bone, and for soft tissue sarcoma 13% and 15%.

Conclusions:
The 5 year survival rate amongst patients who have pulmonary metastasectomy is higher than that observed among unselected registry data for patients with any metastatic disease at diagnosis. There is no evidence that survival difference is attributable to metastasectomy. No data were found on respiratory or any other symptomatic benefit. Given the certain harm associated with thoracotomy, often repeated, better evidence is required.

Article summary

Article focus
• Sarcoma metastases are characteristically blood borne and predominately in the lungs.
• Lung metastases are readily imaged and can be removed, while sparing lung parenchyma, often with minimally invasive techniques.
• Pulmonary metastasectomy for bone and soft tissue sarcoma entered clinical practice about forty years and have become established as a standard of care.

Key messages
• A systematic review of the literature discovered no randomised trial or any other formal attempt to compare survival following pulmonary metastasectomy with what might have been the outcome in similar patients without this surgery.
• There is no evidence in the literature of palliative benefit from pulmonary metastasectomy.
• Detrimental effects on breathing place a limit on repeated and extensive metastasectomy but no beneficial effects are documented.

Strengths and limitations of this study
• The studies retrieved and systematically reviewed are believed by specialists in sarcoma care to be representative of clinical practice and their experience with management of metastatic sarcoma.
• The data retrieved from clinical follow up studies and the cancer registry are so different with respect to which patients are included, and the data elements available for analysis, that any comparisons are tenuous.

Introduction

Pulmonary metastasectomy is a well established component in the management of sarcoma. Metastases may be confined to the lung where, surrounded by air containing lung, they are readily detected on radiographs and are usually surgically accessible. The Cooperative Osteosarcoma Study Group (COSS) found that, of 202 patients who had metastases at diagnosis, 81% had lung metastases and 62% only lung metastases.[1] In an analysis of three European Osteosarcoma Intergroup (EOI) randomised controlled trials of chemotherapy, of 564 patients who had recurrence, 307 (54%) had metastases only in the lung.[2] Osteosarcoma particularly affects the young, who are better able to withstand surgery and, if they can be cured by eradicating the disease, or their survival is substantially lengthened, there are potentially many years of life expectancy to be restored.

The decision to perform pulmonary metastasectomy is usually now made by specialist sarcoma teams and is based on factors such as the interval since surgery, the number and rate of growth of metastases, and their response to chemotherapy. The surgical approach may be videothoracoscopic or by thoracotomy, and surgery may be through staged lateral

thoractomies or bilateral through an anterior approach. The pulmonary resections are also "individualised" depending on the location, size and number of metastases, with an implicit commitment to spare as much lung parenchyma as possible. It may be this degree of variability which makes data tabulation difficult. The authors of the 2011 EOI analysis acknowledged that "Amongst the limitations is the limited information on how the recurrences were treated. However, all patients were treated in experienced sarcoma centres and it is likely that all patients received the best available treatment for their recurrence. This includes, whenever possible, complete resection of a local recurrence and/or surgical treatment of all distant recurrences in case of resectable disease."[2]

In 2006 the UK National Institute of Health and Clinical Excellence (NICE) which issues guidance to the National Health Service in England and Wales, published a manual for commissioners of cancer service on "Improving Outcomes for People with Sarcoma".[3] The manual is more about organization than practice and states that "The management of chest wall, intrathoracic sarcomas and pulmonary metastases requires a combination of skills available from a sarcoma MDT and a thoracic surgeon, often combined with plastic surgical reconstructive skills". Included in this guidance is advice on surveillance for the appearance of pulmonary metastases and states in that context "None of the 21 patients who presented between follow-up visits with symptomatic pulmonary metastases were considered candidates for potentially curative surgical resection of their metastases. Resection of pulmonary metastases was performed for 24 of the 36 patients whose asymptomatic recurrence was discovered by surveillance chest X-ray or staging CT scan"[3] based on evidence reviewed.[4,5] There is evident readiness to operate on asymptomatic pulmonary metastases in sarcoma patients but evidence for the practice, or guidance which patients are believed to benefit, cannot be inferred from this practice manual.

Thoracic surgeons are increasingly being asked to remove lung metastases as part of the overall management for a wide range of cancers. In a survey conducted by the European Society of Thoracic Surgeons (ESTS)[6] practice varied considerably. In particular there was a wide range of opinions on the weight to be placed on factors known to be associated with survival such as the time elapsed since diagnosis of the primary tumour and the number of metastases seen on imaging. This survey was part of a wider programme of work called The European Society of Thoracic Surgeons Lung Metastasectomy Project.[7] In the introduction to the published report the leaders of the project concluded "the level of evidence to support current practice is too low to set firm recommendations to the members of ESTS." At the time of writing up The European Society of Thoracic Surgeons Lung Metastasectomy Project an up to date review of metastasectomy for sarcoma was not available and the report went to press without it. We have therefore undertaken a literature search and a systematic review of pulmonary metastasectomy for sarcoma.

Material and methods

Eligibility criteria.

A literature search was conducted according to PRISMA 2009 recommendations. [8,9] We considered eligible all the articles in the English language, from 1950 to the first week of June 2011, which contained at least 20 patients and any data on surgical outcome(s). Reviews and teaching articles which contributed no data for analysis were excluded. Thames Cancer Registry data were extracted for all cases of bone and soft tissue sarcoma registered from 1985 to 2008.

Types of participant
All patients of any age undergoing pulmonary metastasectomy from any type of sarcoma (bone, soft and mixed series) regardless of first time or repeated.

Type of intervention
First time or repeated metastasectomy from sarcoma.

Information sources.
A Medline search was conducted using OVIDSP interface. Medline web interface at www.pubmed.gov was also searched. The Thames Cancer Registry data was used as comparator.

Electronic Search.
The search expression used was: [lung.mp] AND [metastasectomy.mp] and [sarcoma.mp].

Study selection.
One author (MS) evaluated the reports quality from titles and abstracts identified from the electronic database searches according to the pre-defined eligibility criteria. Full text articles of studies of potentially relevant studies that met the inclusion criteria were retrieved to assess definite eligibility for inclusion.

Data collection process.
The data was extracted by 2 of the authors (MS, FF) independently and then checked by another author (TT).

Data items.
The selected papers were searched and, where available, data were extracted with respect to:

- Research methodology employed
- The purpose of the study
- The patient population from which pulmonary metastasectomy patients were drawn
- Inclusion and exclusion criteria
- Demographic data on patients selected and reported
- The interval between primary surgery and diagnosis and pulmonary metastasectomy
- Chemotherapy use
- Surgical approach, whether open or videothoracoscopic

- Surgical techniques employed
- Survival data
- Statistical analyses of factors related to outcome
- Consideration of second and subsequent metastasectomy operations
- Symptoms and respiratory performance

Thames Cancer Registry data were extracted for stage, data on interventions, sex ratio, median age and survival.

Results

The search returned 98 articles. In addition the reference lists of all papers were searched. We retrieved a further 17 articles, to make the total up to 115 having excluded duplicate records by title, authors or DOIs. Sixty five articles were excluded by title and/or abstract according to the specified criteria. The full text of the remaining 50 articles was retrieved. A further 32 were further excluded because they did not meet the initial criteria after full text review or duplicated data.

We retained 18 articles published since 1990 for inclusion in the systematic review: five report on first and subsequent pulmonary metastasectomy for bone sarcoma, [10-14] six on soft tissue sarcoma, [15-20] and four on mixed sarcoma series.[21-24] The information in Tables 1, 2, 4, and 6 are extracted from these 15 studies which include data on the patients' first pulmonary metastasectomy. Three of the 18 are confined to repeat pulmonary metastasectomy.[25-27] One of these[27] contained 14 patients rather than the specified minimum of 20 patients but is a further report providing outcomes for repeat metastasectomy of some of the patients reported from the same institution and was therefore included.[13]

With respect to research methodology, there were no randomised controlled trials. There was one comparison study in which patients who had undergone videothoracoscopic resection were matched with patients who had undergone a thoracotomy approach.[24] There were no protocol based prospective studies. There was one retrospective cohort study of data obtained from a Cancer Centre's institutional Tumor Registry.[11] In other reports, cases were identified from databases which were held, as far as we could determine, at an institutional level[10,12-17,20,23,26,27] or departmental level. [18,19,21,24,25] It appears that many of the clinical data were retrieved by retrospective case note review. A statement in a report from the M D Anderson Cancer Centre (MDACC) is probably representative of the approach to data collection: "A prospective surgical database was used to identify metastasectomy patients and missing clinical data were supplemented in a retrospective manner."[23]

In most studies the stated purpose of analysis was to report survival following first [10-21,23,24] or repeated pulmonary metastasectomy.[22,25-27] In ten of the 18 reports, statistical analyses were performed to identify patient and tumour characteristics associated with improved survival following first pulmonary metastasectomy. [11,13,14,16,18,19,21,23,25,26]

The population from which the patients having pulmonary metastases were drawn, is given in seven publications.[10-12,14,15,17,23] (Table 1) As can be seen from the footnotes to the table, no two denominators are defined in the same way and none are comprehensive at a community level. Some authors give an upper age limit (not more than 55 years,[12] 40 years,[14] or 20 years[11]) but read in context this appears to be to match the data set of operated patients rather than a prior policy. Some series include all sites while others are limited to limbs[10,12] or trunk and limbs.[11] They variously include all sarcoma patients,[23] or only those with soft tissue sarcoma.[17] The proportion of the denominator population recorded as developing pulmonary metastases ranges between 18% to 50% while the proportion of those with pulmonary metastases who have an operation to remove them varied from 5% to 88%. The report with the largest data set (MDACC) [23]) reported that only 1% of sarcoma patients have a pulmonary metastasectomy. We have not found it possible to determine how much of the variation in the recorded data is attributable to varying selection in clinical practice, the different biology of tumours according to histology, tumour site, or variation amongst patients. A large amount of the variation appears to depend on how wide the net is cast in capturing the denominator.

Amongst these 18 studies of pulmonary metastasectomy for sarcoma the inclusion criteria are much as those proposed by Thomford [28] that the cancer at the primary site was eradicated, controlled, or amenable to control;[10,12,13,15,17-22,24,26,27] that the metastatic lung disease was amenable to complete resection;[10,11,13,15,18-21,24,26,27] that there was no metastatic disease elsewhere;[10,12,13,15,17-22,24,26,27] and that the patient was expected to withstand the loss of lung tissue necessary to give clearance.[10-12,15,17-22,24,26,27] In individual instances authors specified that there should be no mediastinal or chest wall involvement;[17] absence of pericardial or pleural effusions;[12] that the overall operative risk was acceptable;[26] or that there was no other available more effective treatment.[19] In one report, increased size on chemotherapy was allowable, but not an increase in the number of metastases.[24] One study with five subgroups gave group by group criteria which, read in context, appeared to defined after exploration of the available data to facilitate analysis and reporting.[23] Criteria for inclusion or exclusion in the metastasectomy cohort were not found in three studies.[14,16,25]

Data are given in Table 2 for the 15 studies which include data on the first pulmonary metastasectomy, for a total of 1168 patients. The average age of bone sarcoma patients was 17 years based on 377 patients in four studies with calculable data [10,12,13], excluding the reports limited to patients aged <21 years[11] or <40 years.[14] For soft tissue sarcoma the average age was 46 based on five studies including 277 patients[16-20] excluding a study where median and range were given.[15]

Male sex was predominant in bone sarcoma (65% of 532 patients) but not in soft tissue sarcoma reports (50% of 277 patients). These differences in age and sex preclude meaningful amalgamation of outcome data following pulmonary metastasectomy for bone and soft tissue sarcoma.

The interval between resection of the primary and first pulmonary metastasectomy was provided in 9/15 reports and was highly variable as can be seen from Table 2. There is a degree of consistency in the median interval of 1-2 years but half of the authors providing data, operated on synchronous metastases (5 of 10). Repeat metastasectomy was performed in 43% of patients based on 14/18 reports in which the data could be extracted. (Table 3)

Chemotherapy was frequently used but schedules were variable both within and between publications. Some authors stated that preoperative and/or post operative chemotherapy was given routinely in all cases[10,21,26,27] but more often the practice varied. [11-14,16,18,21] One paper states "The only constant was that when the disease-free interval was <2 years with a single lung metastasis, no chemotherapy was added to surgery" and another that it was at the discretion of the oncologist.[19] One group used chemotherapy preoperatively only when there were six or more metastases.[17] It was also implicit in the text of several papers that response to chemotherapy was part of the clinical evidence used to help select patients for surgery; non responding and progressing patients were less likely to be selected for pulmonary metastasectomy and this information is not necessarily explicit in the report. This statement in the report from the MDACC is representative of this approach: "Those who developed metastatic disease early with multiple pulmonary nodules were treated initially with chemotherapy to determine the pace of disease progression, if any, on treatment. Patients responding to chemotherapy, those with stable disease, and those with slow progression were referred for resection while those with rapidly progressive metastatic disease received alternative chemotherapy treatment."[23]

Whether videoscopic or open surgery was used, and if open through what incision, and the surgical technique used to resect the metastases, are summarised in Table 4 for 12/15 papers including data on first metastasectomy operations.[10-13,16-21,24] The remaining three of the 15 studies were not explicit with respect to the surgical approach. In the more common surgery for carcinoma metastasised to the lung, lymphadenectomy has become an important consideration.[29] In these reports concerning sarcoma patients, hilar nodes were not routinely dissected[19] or maybe dissected "when necessary".[12] This avoidance of lymphatic resection appears to be linked to the lower rate of lymphatic spread in sarcoma compared with other thoracic malignancy in which further spread from the metastases to mediastinal lymph nodes is frequent.[29]

There is a strong evident preference for open surgery (96% of patients had a thoracotomy of some form) with considerable emphasis placed by several authors on the importance of manual palpation of the lung[10-12,16,17,20,22] which cannot be achieved through a purely videoscopic approach. One study specifically addressed the question for whether the less invasive thoracoscopic approach might be as effective[24] and it was concluded that it might be an option if there are no more than two metastases but this was not derived from data analysis presented in the publication. The general use of thoracotomy, often bilateral, and repeated metastasectomy in 43% of patients overall represents a high treatment burden for patients. (Table 3)

Thames Cancer Registry data for sarcoma were studied to provide some context to the overall survival rates of patients with sarcoma. (Fig.1) The Registry has employed its own 4-level staging system since 1960 and stages around 60% of all solid tumours. The classification system uses information in the patients' notes to determine if the disease is local (stage 1), has extension beyond the organ of origin (stage 2), has regional lymph node involvement (stage 3) or has metastasised (stage 4). Survival data by stage for two complete decades 1985-1994 and 1995-2004 for both bone and soft tissue sarcoma are provided in Fig.1. For patients entered as Stage 4 bone sarcoma (metastatic disease at the time of registration) in those two decades five year survival of 20% and 25% are recorded for bone sarcoma and 13% and 15% for soft tissue sarcoma.

The Registry does not include full data on treatment but does provide data on the highest surgery code. These are presented in an abbreviated form in Table 5. According to the selection criteria set out above, since the stated first criterion for pulmonary metastasectomy was that a radical operation had been successful at the primary cancer site, it is amongst the 8% of bone sarcoma patients and 21% of soft tissue sarcoma patients that pulmonary metastasectomy patients would be found.

Five year survival data are plotted against publication date (Fig.2) and the size of the series (Fig.3) for 14 of these 15 studies where the data are given, to allow for this visual inspection of time or case volume. Three and/or five years survival for the 15 studies including first (and subsequent) metastasectomy data are plotted in Fig.4

Five year survival data are set out in Table 6 sorted by tumour type from 14 of the 15 studies including first (and subsequent) metastasectomy data. Together these provide data on 1196 patients having metastasectomy from as early as 1976 [16] to as recently as 2008.[14] Overall about a third of patients who have had pulmonary metastasectomy for bone sarcoma and about a quarter who have had pulmonary metastasectomy for STS survive beyond five years. Survival data for two complete decades 1985-1994 and 1995-2004 are included in the table to provide a reference measure of survival in all sarcoma patients in the registry who were classified as Stage 4, that is sarcoma metastasized at presentation/registration. Direct comparison cannot be made but it is a reminder that an implicit assumption that the five year survivals of the patients in the pulmonary metastasectomy series would have approached zero would be incorrect. Summary data of sex distribution and the median age for patients in two completed decades (1985-94 and 1995-2004) with bone and soft tissue sarcoma in Table 7.

We can reasonably deduce

1. that five year survival after pulmonary metastasectomy is not necessarily attributable to the metastasectomy
2. that five year survival does not equate to cure since there are five year survivors with metastatic disease.

Data are not available in the publications concerning the fate of patients beyond five years and there are no narrative accounts of the clinical course of these patients. However a number of the authors include, in their narrative, a statement of belief in cure for patients who have recurred in the lung or that their surgery has curative intent[12,14,16,17,19,24,25] and the phrase "potentially curative resection" is included in NICE guidance.[3] Illustrative statements from recent publications are these from 2009 and 2010:

"Given the lack of effective systemic therapies, PM remains the only potentially curative treatment for STS lung metastases as long as all known disease can be completely resected with negative margins."[16]

"We demonstrate that after repeated metastasectomies, a subset of patients can be cured."[14]

Other author explicitly exclude likelihood of cure attributable to pulmonary metastasectomy. Antunes writes "The 5-year survival may reach 50%, although true cure is extremely rare, the majority of patients eventually dying of the disease."[10] And Sardenberg and colleagues state "It should be emphasized that surgery does not change the biology of the tumor or the metastatic process, and a definitive cure for most patients represents the combination of host histology, tumor spread, response to systemic therapy, and surgical resection, which together render the patient free of disease."[19]

Several reports include multivariate analysis to seek factors that might determine a greater or lesser survival rate. The interval between diagnosis or resection of the primary cancer and the metastasectomy surgery is the commonest factor reported as being significant [11,18,19,21,23,25,26] survival usually being better if the interval was 12 months or longer. Fewer metastases was also associated with better survival [13,14,18,19,23,25,26,30] most commonly at a number of about three or fewer. Female sex [14,16] was also favourable. Patients in whom there was substantial necrosis following chemotherapy survived longer.[10,11,14,22]

No data were found regarding respiratory function or symptoms in any of the 18 reports. Where mention was made of respiratory function in the text it was related the decision to operate. Several authors explained that a point had been, or might be reached, where respiratory function or respiratory reserve precluded further metastasectomy. No measurement of this or its consequences for the patients was provided in any report.

Discussion

A major limitation, when interpreting reports of pulmonary metastasectomy for sarcoma, is the absence of control data. It is usual in surgery to rely heavily on evidence from case series, either in the form of retrospective case note reviews or less commonly prospective cohort studies. When there is a clear temporal and mechanistic relationship between cause and effect, and the signal is evident from the noise, observational studies often provide sufficient evidence.[31] The simple evidence of cause and affect cannot be

invoked where there is a widely variable time course and multimodal treatments as is the case in protracted, repeated and multimodal treatment of sarcoma.

Efficacy, effectiveness, and cost effectiveness are different measures of the benefits of a treatment. Pulmonary metastasectomy has been shown to be efficacious in that complete macroscopic clearance has been achieved; in appropriately selected cases, R0 resection of all known pulmonary metastases can be consistently accomplished. Whether pulmonary metastasectomy is effective in prolonging life requires proof that survival has been extended, by metastasectomy, beyond that which would have occurred without pulmonary metastasectomy. Cost effectiveness requires, in addition to survival, measures of health gained, measures of health lost due to death and complications, and for these to be costed in comparison with any alternatives, including no treatment. This third measure, estimation of cost effectiveness is outside the scope of this review and depends on first establishing effectiveness.

Evaluation of the effectiveness in preventing or postponing death by pulmonary metastasectomy is the common objective in these clinical reports. The existing practice is believed to be effective based on repeated experience world wide for over forty years. In 1971 thoracic surgeons at Memorial Sloane Kettering reported on 22 patients with treated osteogenic sarcoma in whom they performed lung resections. [32] The meticulous case by case communication of that experience merits revisiting. (Fig.2)

In the discussion that followed Beattie modestly states:
"We reported these data with some reluctance, since they really constitute a progress report on a clinical research project underway at Memorial Hospital. We used osteogenic sarcomas because they are such serious tumors. There are occasional spontaneous regressions and good results; but you saw in the figures Dr. Martini showed that with amputation we have had a 17% five-year cure rate. Of the 83% of patients who died, 5% lived three years. Very occasionally a patient would go on longer before dying."[32]

Twenty-years later [33] Beattie reported further:
"Twenty-year follow-up reveals that at least four of the six survivors at 10 years survived more than 19 years; one was lost to follow-up. The patient who died of metastatic osteogenic sarcoma more than 19 years after her first thoracotomy had a total of nine thoracotomies."

An implicit assumption is embedded in many subsequent reports that none of these patients would have lived beyond five years without metastasectomy. There are other reasons, apart from having had pulmonary metastasectomy, for patients with pulmonary metastatic disease to be alive at and beyond five years. These patients are carefully selected and although it is not possible to put a reliable figure on it, they are a minority of all patients with the disease.[2] (Table 1) It is appropriate to select patients for surgery and yet comments such as "survival of (surgically treated) patients was significantly better than of patients ineligible for metastasectomy. P<0.00001"[14] is not an appropriate or meaningful statistical comparison: the difference is evident but how much is due to the selection and how much to the surgery, cannot be determined.

The identifiable factors for selection of suitable patients include fewer metastases and a longer interval between the diagnosis and treatment of the primary and the resection of pulmonary metastases.[34,35] Others which appear in some analyses are tumour doubling time and the size of the nodule(s) which under surveillance is a proxy for rate of growth. These are prognostic features for survival under any circumstance. We also know from the Thames Cancer Registry data that there are 20-25% of patients with osteosarcoma and about 15% with soft tissues sarcoma, with metastases at the time of registration, who are alive beyond five years. (Table 6) The narrative accounts record that there are some natural long term survivors: "one patient not operated on remains alive 18 years after not having surgery."[14] "Long-term survivors appear to belong to a subset of patients with indolent, lung-only disease."[36] These natural survivors, who are likely to have slower progression, and fewer metastases, are likely to be disproportionately frequent amongst patients selected for metastasectomy [37] as seen in the graphical depiction, for the selection process is not random. (Fig.6). More than thirty years ago Aberg first proposed that selection might be the major factor determining survival after pulmonary metastasectomy [38] and returned to this question in 1997. [39] It is of note that none of the authors cite Aberg. It is known that "citation distortions create unfounded authority" [40] and citation network analysis.[41]

In fact the effect of selection may easily be underestimated. Multivariable analysis cannot detect more than a limited number of factors in these relatively small series. All of these factors may exhibit covariance and they are all indices of the relative aggressiveness of a cancer. Failure for one or more of these factors to reach significance in any particular Cox model does not refute the overall finding. Furthermore, if the knowledge of previous finding leads to the exclusion of some patients, the range of that variable is reduced and it is less likely to be found in subsequent analyses. [42]

In this group of young and therefore physically resilient patients there seems to be a strong desire to never say no, and to push the boundaries for selection for metastasectomy. It is well established that patients with more metastases are unlikely to live long after metastasectomy. Nevertheless there is no apparent upper limit in many of the reports nor was there for 85% of surgeons in the ESTS survey.[6] Amongst the reports pulmonary metastasectomy in the present systematic review some surgeons report very high numbers of metastases resected. For example "The authors have removed as many as 80 to 100 nodules during a single thoracotomy" [22] and in the COSS report "The highest number of pulmonary nodules surgically removed was 250"[1] are out of line with the observational evidence that above a count of relatively few metastases, outcomes are too poor to justify this surgery. Maybe these high numbers reflect the observation that the preoperative count of nodules underestimates the true extent of the disease "It is interesting that despite the presence of only three or four nodules on many CT scans, up to 50 or more nodules were found and removed in a number of these patients."[22] The issue of the relative reliability of modern imaging versus surgeons' palpation of the lung has been considered elsewhere with varying conclusions.

The extent of necrosis caused by chemotherapy evident in the excised nodule was found to be a favourable feature for survival.[10] The clinical response or failure to respond to chemotherapy was given as factor in selection in several series. Both of these observations are evidence that chemotherapy is having an effective in these patients and has had a demonstrable effect on their disease. Why then should a survival difference be attributed to the surgery?

There is a firm belief that if sarcoma recurs in the lungs, and the patient is still within the criteria for resection, further resections should be performed. "The authors concluded that patients persistently free of the primary osteosarcoma who developed recurrent resectable metastatic disease of the lung should be considered for reoperation a second, third, or fourth time, as these patients had similar DFI curves after five-years."[26] This belief is supported by what might be inappropriate data interpretation. Consider these statements for example: "Prognostic factors for increased survival included 3 or greater redo pulmonary operations"[23]; "patients with complete resection for recurrent pulmonary metastasis show a significantly better prognosis after repeat pulmonary metastasectomy"[27] and "repeat metastasectomy for recurrent pulmonary metastasis also provided a favorable overall survival (P <0.041)".[20] To undergo a second metastasectomy a patient has to have survived, and been without evidence of disease for a reasonable length of time, to meet the criteria for each subsequent operation. The problem is exemplified by Sardenberg and colleagues. Survival was measured from the first thoracotomy for pulmonary metastasectomy (confirmed with the first author) and was 15 months, 45 months and 48 months, in 35 patients having only one surgical episode, 24 who had two and 13 who had three. The authors provide a statistical analysis (P=0.077) of the association between more thoracotomies and longer survival. They neglect the fact in their interpretation that survival after surgery, and for a reasonable period of time, was a requirement to move to the next analytical group.[19] This way of presenting the data maximizes survivor bias: ongoing survival is an entry criterion to having a further metastasectomy operation.

We found no of data, or even a narrative account, concerning the effect of surgery on symptoms. The patients who are regarded as candidates for metastasectomy are generally detected on surveillance and presentation with symptoms probably distinguishes patients as being not suitable for metastasectomy, either because it represents extrapulmonary disease of the pulmonary disease is too advanced. The evidence cited in NICE guidance[3] is as follows: "Detection on the basis of symptoms occurred in 21 patients. Fifteen of these patients presented between scheduled visits. Seven patients were symptomatic primarily on the basis of their metastatic pulmonary disease. These patients had diffuse metastatic disease in all cases, with documented synchronous recurrence outside the lung, and none was resectable."[5] What is implicit in many of the reports reviewed is that ultimately they call a halt to repeated thoractomies because the patient respiratory function will not withstand further surgery and loss of lung tissue.

Two publications[45,46] which appeared in 2011 after completion of our review and data analysis, and following submission, have been brought to our attention. They come from prominent North American institutions and appeared in a specialist thoracic surgical

journal Annals of Thoracic surgery. The report from Brigham and Women's Hospital, Boston, Massachusetts states in its title "Repeated and aggressive pulmonary resections for leiomyoma metastases extends survival". The report is of 82 patients with a variety of bone and soft tissues sarcomas between 1989-2004. Repeat metastasectomy was performed in 28/82 with some patients having 3, 4 or 5 thoracic operations. Operated patients with leiomyosarcoma 31/82 had a median survival of 70 months compared with 24 months for other sarcoma subtypes. No control data for survival amongst comparable patients not operated upon are provided. The text confirms that the surgery was repeated and aggressive but that survival was extended as a result cannot be inferred from the data presented for the reasons given already. The report from Massachusetts General Hospital is of 97 patients with 13 sarcoma subtypes operated on for pulmonary metastases between 2002 and 2008.[46] They report that of 69% of 29 patients who had multiple operations were alive at five years compared with 41% of 60 patients who had a single operation and find the difference to be statistically significant and the bottom line of the conclusions reads "Repeated pulmonary metastasectomy in select patients may improve survival despite recurrent disease." But patients have first to be survivors to be candidates for surgery, a point the authors make themselves in their discussion "Patients in whom disease rapidly recurred after surgery (either as a local recurrence or disseminated disease) were probably selected out from repeated surgical resection."[46] Neither of these papers provides evidence on symptomatic benefit for these patients.

While there are some long term survivors amongst those who have this surgery the absence of control data leaves Aberg's challenge[38,39] unrefuted. His hypothesis was that patients destined to survive longer are more likely to be selected for surgery and it is the process of selection, rather than the effect of pulmonary metastasectomy, that is responsible for any survival difference perceived. Although it would be challenging to perform, a randomised controlled trial may be necessary if we are to see the signal from the noise in this area of clinical practice.

Legends to figures

Figure 1
Thames Cancer Registry data. Kaplan Meier survival plots by stage for decades 1985-1994 (above) and 1995-2004 (below) for bone (left) and soft tissue sarcoma (right). Stage 4 (that is metastasised at the time of diagnosis/registration) in red.

Figures 2
Five year survival rates plotted against the publication date.

Figure 3
Five year survival rates plotted against the size of the series.

Figure 4
Three and five year survival rates from publications in Table 6. (Bone sarcoma red, soft tissue sarcoma green and mixed series blue.)

Figure 5
The full display of essential features of the patients and their with survival from primary resection to metastasectomy and subsequently. From Martini et al 1971

Figure 6
A conservative estimate of natural five year survivors is set at 5% (15/300 in this depiction) and they are in green. Ranking patients on the Y and X axes from least to most favourable based on fewer metastases and longer interval since diagnosis might have the effect of clustering these natural survivors as shown. If selection for surgery is also based on these factors, it might be the selection rather than the surgery which is associated with a higher than anticipated survival rate shown here as 10/25 or 40%.

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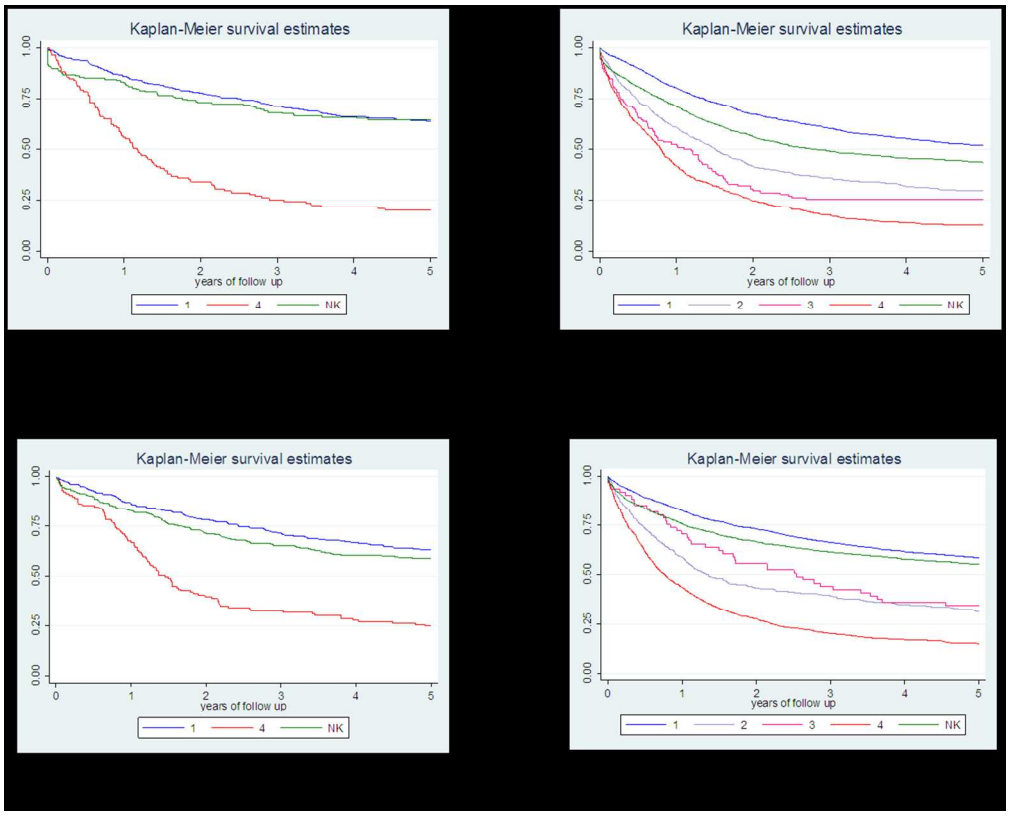
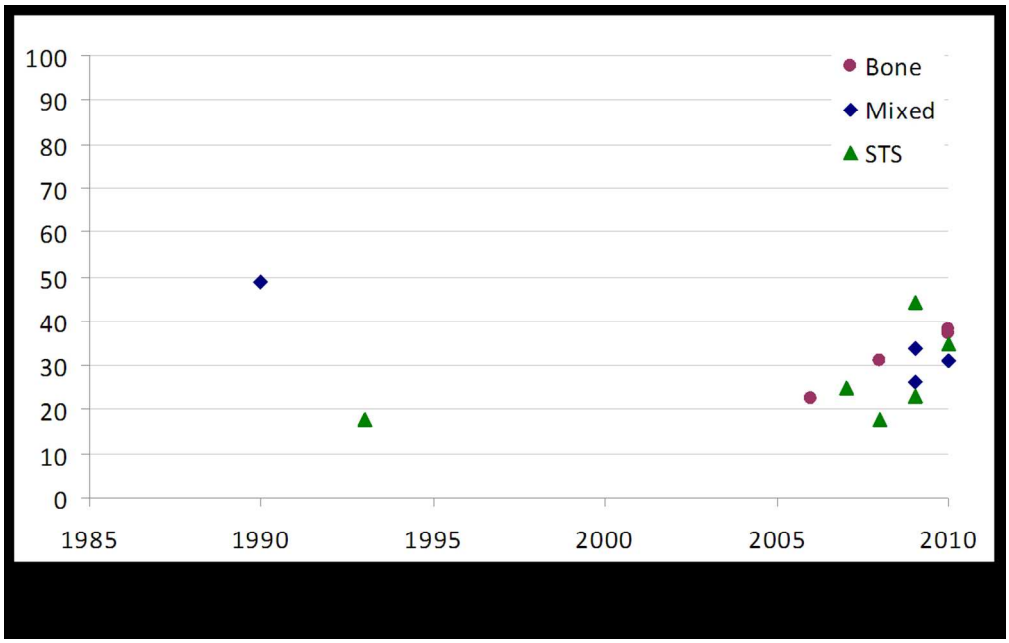


Figure 1
Thames Cancer Registry data. Kaplan Meier survival plots by stage for decades 1985-1994 (above) and 1995-2004 (below) for bone (left) and soft tissue sarcoma (right). Stage 4 (that is metastasised at the time of diagnosis/registration) in red.

214x172mm (150 x 150 DPI)



Figures 2
Five year survival rates plotted against the publication date.

228x144mm (150 x 150 DPI)

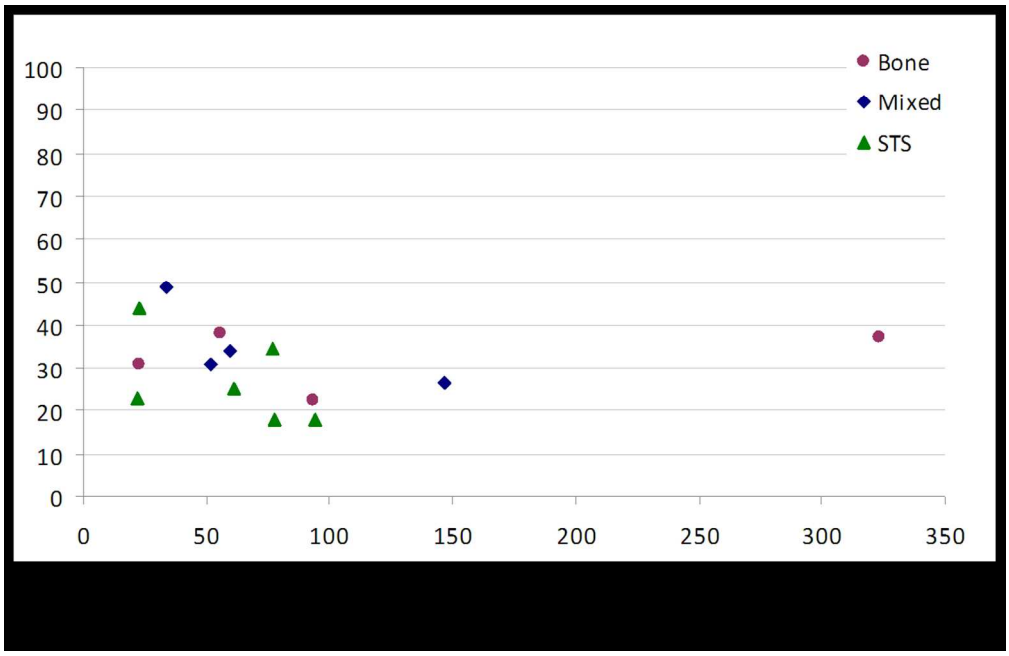


Figure 3
Five year survival rates plotted against the size of the series.

224x144mm (150 x 150 DPI)

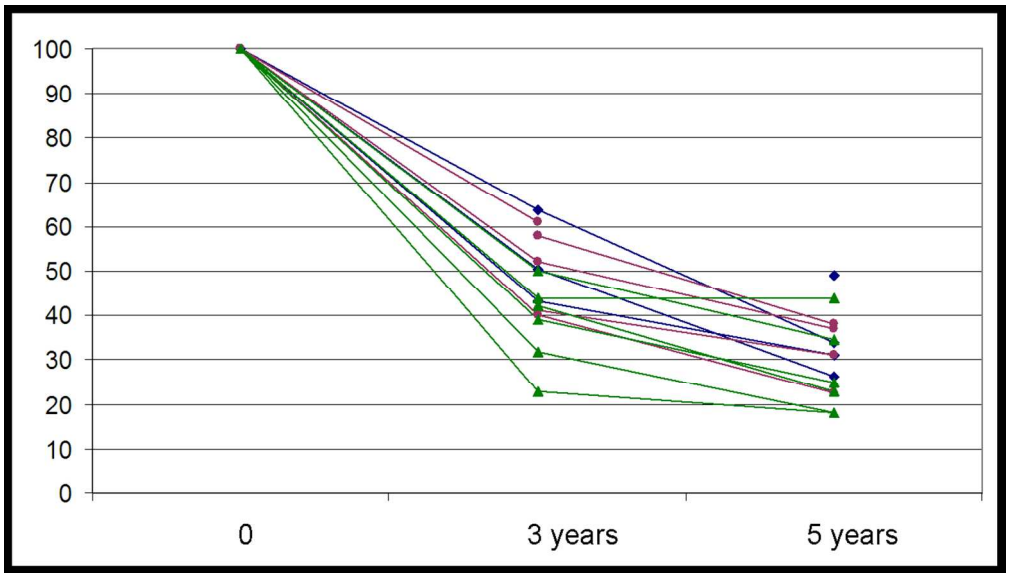


Figure 4
Three and five year survival rates from publications in Table 6. (Bone sarcoma red, soft tissue sarcoma green and mixed series blue.)

226x127mm (150 x 150 DPI)

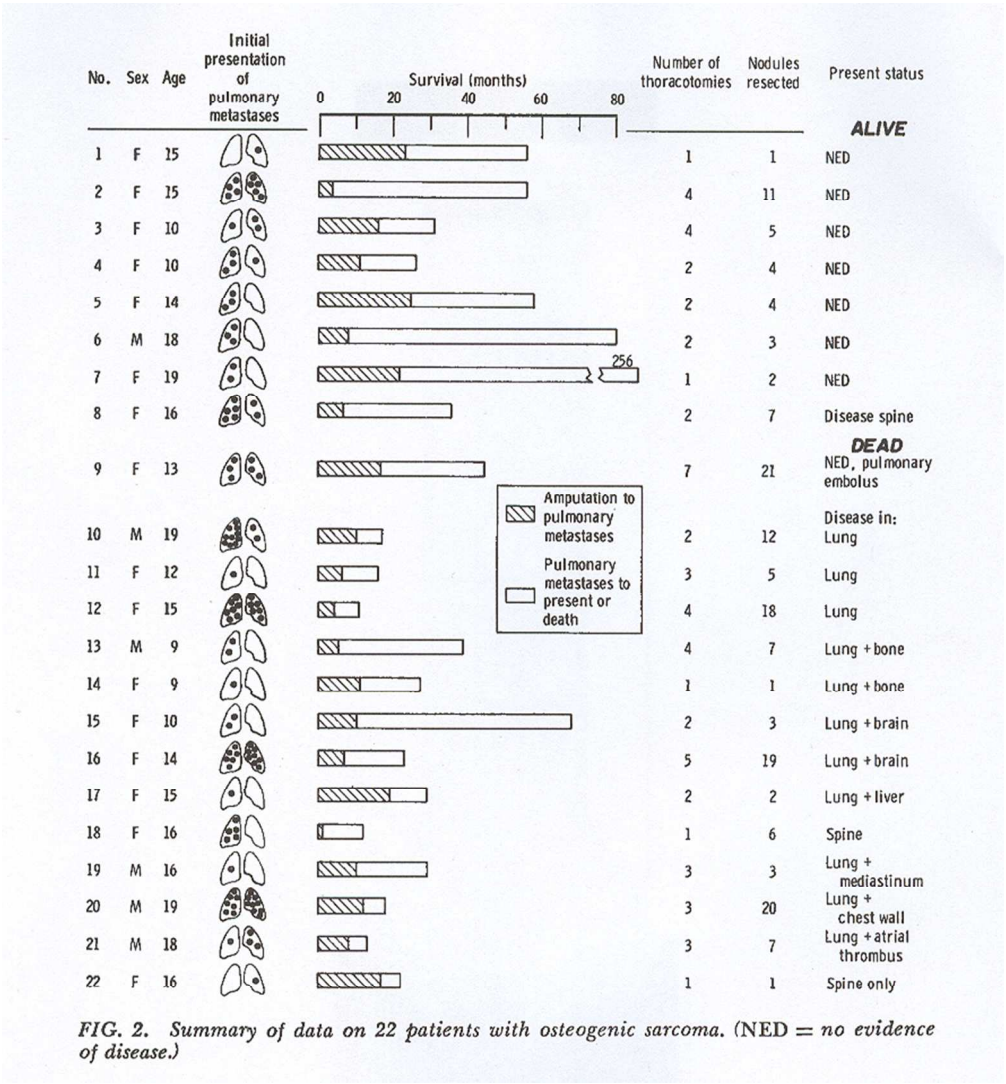


FIG. 2. Summary of data on 22 patients with osteogenic sarcoma. (NED = *no evidence of disease.*)

Figure 5
The full display of essential features of the patients and their with survival from primary resection to metastasectomy and subsequently. From Martini et al 1971

150x161mm (150 x 150 DPI)

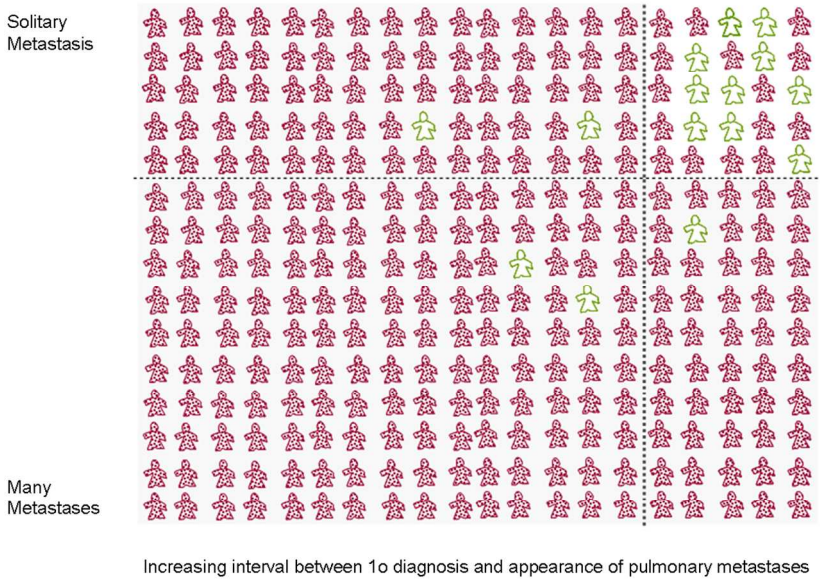


Figure 6
A conservative estimate of natural five year survivors is set at 5% (15/300 in this depiction) and they are in green. Ranking patients on the Y and X axes from least to most favourable based on fewer metastases and longer interval since diagnosis might have the effect of clustering these natural survivors as shown. If selection for surgery is also based on these factors, it might be the selection rather than the surgery which is associated with a higher than anticipated survival rate shown here as 10/25 or 40%.

235x176mm (150 x 150 DPI)

Publication	Histo	Start Date	End Date	All registered sarcoma patients A	Patients with pulmonary metastases B	Pulmonary Metastasectomy as reported in cited papers in systematic review C	Proportion of sarcoma patients with pulmonary metastases (=B/A)	Proportion of Patients with pulmonary metastases who have metastasectomy (data as in reports) (=C/B)	Proportion of all sarcoma patients who have pulmonary metastectomy (=C/A)
Antunes 1999	Bone	1989	1997	198[a]		31			16%
Harting 2006	Bone	1980	2000	272[b]	137[c]	99	50%	72%	36%
Briccoli 2010	Bone	1985	2005	1197[d]	369[e]	323	31%	88%	27%
Buddingh 2009	Bone	1990	2008	197[f]	88[g]	56	45%	64%	28%
Gadd 1993	STS	1983	1990	716[h]	135[i]	78	19%	58%	11%
Rehders 2007	STS	1991	2002	678[j]	121[k]	61	18%	50%	9%
Blackmon 2009	Mixed	1998	2006	15744[l]	4355[m]	234	28%	5%	1%

Table 1 Data from reports providing the number of patients from which the study population was derived

[a]patients operated on for osteogenic sarcomas of the limbs were followed in their centre
[b]patients with osteosarcoma of the trunk or extremities who were younger than 21 years and who had medical records available for review
[c]developed or presented with radiographically evident pulmonary nodules. These 137 patients formed the initial study cohort.
[d]patients with histologically proven HGOS of the extremity 55 years old or younger diagnosed at their Institution
[e]first recurrence with metastases located only in the lung
[f]patients under the age of 40 treated for high-grade OS at the Leiden University Medical Center
[g]patients who had pulmonary metastases either at diagnosis or during follow-up
[h]adult patients with a primary or locally recurrent extremity soft tissue sarcoma admitted to MSKCC
[i]patients with pulmonary metastases
[j]patients with STS were treated at the Department of Surgery, University Hospital
[k]pulmonary metastasis of STS occurred during follow-up,
[l]patients with soft tissue and bone sarcoma referred to The University of Texas M.D. Anderson Cancer Center
[m]patients diagnosed with sarcomatous pulmonary metastases

Author	Sarcoma patients who have pulmonary metastasectomy (N)	Age mean (years)	Age range (years)	Sex Males	Sex %male	Median interval between primary and metastases (months)	Range (months)	Mean number of mets resected	Range
Bone									
Antunes 1999	31	25	10-54	21	68%	22	4-122	3.2	1-8
Harting 2006	99	13.9	+/- 4.2	67	68%	0 in 17%	0-NF		1->10
Briccoli 2010	323	16	4-55	201	62%	NF		NF	NF
Chen 2008	23	19	6-68	15	65%	19	0-108	5.0	
Buddingh 2010	56	NF	NF	40	71%	NF			
Soft Tissue									
Gadd 1993	78	(55)*	17-85	NF		14	1-152	NF	NF
Smith 2009	94	49	9-75	47	50%	15	0-NF	2.5	1-105
Rehders 2007	61	42	18-47	33	54%	21	0-3	5.0	1-48
Garcia Franco 2009	22	41	13-82	10	45%	18	5-84		
Sardenberg 2010	77	45	NF	37	48%	NF		3.5	
Chen 2009	23	53	15-86	12	52%	NF	0-168		
Mixed									
Snyder 1991	34	23	NF	20	59%	19	<6->24	11	NF
Blackmon 2009	234	<50*		123	53%	Varied	NF	NF	NF
Gossot 2009	60	40		34	57%	18	NF	NF	NF
Garcia franco 2010	52	20	5-74	31	60%	20	5-189	NF	NF

Table 2 Summary data on 15 papers reporting on series of patient undergoing a first pulmonary metastasectomy operation for sarcoma.
* median age
NF means data were not found

Series	N 1st	N 2nd	Multiple
Rehders 2007	61	13	21%
Antunes 1999	31	8	26%
Garcia franco 2010	52	16	31%
Garcia Franco 2009	22	7	32%
Chen (EJSO) 2009	23	8	35%
Smith 2009	94	33	35%
Briccoli 2005	267	94	35%
Briccoli 2010	323	122	38%
Buddingh 2010	56	26	46%
Sardenberg 2010	77	37	48%
Gossot 2009	60	33	55%
Blackmon 2009	234	141	60%
Chen (EJCTS) 2008	23	14	61%
Snyder 1991	34	28	82%

Table 3. The proportion of patients who have second or subsequent metastasectomy. This does not include staged bilateral thoracotomies which are regarded as a single intervention. Reports are ranked according to the proportion having second and subsequent metastasectomy interventions. Sequential staged operations (for example lateral thoracotomies planned with an interval of 1-3 weeks) are considered by the authors as a single episode of treatment.

Report	Surgical approach	Surgical technique
Snyder 1991	Thoractomy Bilateral disease staged thoracotomy, 1-2 weeks interval 16/34	Enucleation
Antunes 1999	Thoracotomy 30/31 Median sternotomy 1/31	Enucleation Wedge resection Lobectomy
Harting 2006	Thoracotomy, Staged or simultaneous bilateral thoracotomies Median sternotomy	
Briccoli 2010	Thoracotomy Bilateral thoracotomies	Wedge resection Lobectomy Pneumonectomy
Garcia Franco 2010	Thoracotomy 30/52 Sequential bilateral thoracotomy 7/52 VATS) 10/52 Clamshell 5/52	Wedge 44/52 Lobectomy 6/52 Exploratory thoracotomies 2/52[i]
Chen 2008	Thoracotomy	Wedge 22/23 Lobe 1/23
Smith 2009		Wedge 74/94 Lobectomy 17/94 Pneumonectomy 3/94 Resection of other thoracic disease 16/94
Rehders 2007	Thoracotomy 29 (48) Bilateral thoracotomy, 2 sessions 10 (16)[ii] Median sternotomy 22 (36)	Wedge resection 52 (85) Lobectomy 9 (15)
Garcia Franco 2009	Thoracotomy 19 VATS 2 Sternotomy 1	Wedge 19 Lobectomy 3
Sardenberg 2010	Thoracotomy Staged bilateral thoracotomy	Complete resection with 10mm margin
Chen EJSO 2009		Wedge resection 21/23 Lobectomy 1/23 Pneumonectomy 1/23
Gossott 2009	Thoracotomy 29 VATS 31 In a comparative study of the two approaches	

Table 4 Surgical approaches and resection techniques in reports of 1st time pulmonary metastasectomy

[i] That is to say no resection of sarcoma was performed in these patients.
[ii] These patients have planned sequential operations about two weeks apart and it is regarded as a single intervention as opposed to a repeat metastasectomy operation.

	Bone		STS	
	N	%	N	%
Total removal of organ, or operation stated to be radical	145	8%	3203	21%
Partial or debulking operations on the primary tumour	648	35%	4935	32%
Lymphadenectomy	2	0.1%	171	1%
Non-tumour removing surgical treatment	160	9%	245	2%
Haematological procedure (e.g. bone marrow transplant)	2	0.1%	19	0.1%
Investigative procedure only	298	16%	2072	14%
Type of surgery not known	11	1%	59	0.4%
No surgery recorded	581	31%	4559	30%
	1847	100%	15263	100%

Table 5 Highest Surgery Code of Thames Cancer Registry sarcoma patients 1985-2008

Author	Sarcoma patients who have pulmonary metastasectomy (N)	Five year survival where provided	Middle date of metastasectomy series and date ranges for TCR
Bone			
Harting 2006	93	23%	1991
Briccoli 2010	323	37%	1996
Chen (EJCTS) 2008	23	31%	1999
Buddingh 2010	56	38%	2000
TCR		20%	1985-1994
TCR		25%	1995-2004
Soft Tissue			
Gadd 1993	78	18%	1987
Smith 2009	94	18%	1989
Rehders 2007	61	25%	1997
Sardenberg 2010	77	35%	1999
Chen (EJSO) 2009	23	44%	1999
Garcia Franco 2009	22	23%	2002
TCR		13%	1985-1994
TCR		15%	1995-2004
Mixed			
Snyder 1991	34	49%	1984
Garcia franco 2010	52	31%	2002
Blackmon 2009	234	26%	2003
Gossot 2009	60	34%	2004

Table 6 Five years survival and Thames Cancer Registry summary data

Five year survival from 14 of the 15 studies reporting first (and subsequent) pulmonary metastasectomy operations. They are grouped by sarcoma type and then by mid year of the series to aid visual inspection for time trends. Thames Cancer Registry (TCR) five year survival data for Stage 4 patients are provided for two complete decades of data overlapping the reported series. These TCR patients all had metastases at presentation but not necessarily lung or lung only.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5*6-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19/28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Year	Cases	M/F ratio	Median age
Bone			
1985-1994	762	1.31	35
1995-2004	709	1.35	33
Soft tissue			
1985-1994	5615	0.98	56
1995-2004	6256	0.82	58

Figure 7

Sex ratio and median age of patients in Thames Cancer Registry for whom survival data are provided in Table 6.