# Extending Surgery for Pulmonary Metastasectomy
## *What Are the Limits?*

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**Introduction:** The purpose of pulmonary metastasectomy is to remove all known remaining cancer with the purpose of cure or to lengthen survival. Little information is available on the extent of surgery that is justified and or on reasonable evidence based limits to the extent of surgery.

**Methods:** A systematic review was designed to evaluate the role of extended surgery in the treatment of lung metastasis. For this analysis, the following three research questions were formulated.

Q1) Is pneumonectomy indicated for pulmonary metastasectomy?
Q2) What is the number of repeat operations justified and what might be the criteria?
Q3) What number of individual metastases is it justified to remove in a single procedure? A MEDLINE search of English language articles was conducted using key words appropriate to the three questions posed. We excluded reports with little or no data, single cases, small series, and review articles without data.

**Results:** Most information concerning extremes of surgery is in the form of case reports, small series, or sporadic cases within a retrospective report of a larger group of patients undergoing pulmonary metastasectomy. Meta-analysis was ruled out because of the insufficient quantity and quality of data in the available literature.

Q1) extended resection for pulmonary metastasis is feasible and may be justified in individualized circumstances. We believe caution is warranted before performing pneumonectomy because it is debatable whether any possible benefit justifies the adverse consequences of this surgery and long-term survival is poor.
Q2) multiple attempts to re-establish intrathoracic control of metastatic disease supported by some authors in carefully selected patients, but apparent benefit may be a result of survivor bias, and the ratio of harm to benefit is likely to increase with each subsequent attempt.
Q3) if on accepted criteria specific to the primary cancer the patient is a candidate for pulmonary metastastasecomy, then the goal should be to resect all metastases that are there, irrespective of the number. However, with increasing pulmonary metastatic count, there is less good survival and greater loss of lung tissue. These issues should be fully considered at the planning stage.

**Conclusions:** Evidence-based recommendations for extended treatment of lung metastasis are at best weak. We have summarized the available data to provide the most up to date information regarding extended surgery in an attempt to define limits in the treatment of lung metastasis.

**Key Words:** Colorectal, Pulmonary metastasectomy, Sarcoma.

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The purpose of pulmonary metastasectomy, with few exceptions, is to achieve cure or to lengthen survival, by removing all known remaining cancer for that patient. It is usually undertaken in the absence of symptoms attributable to metastatic disease so other than in individual and uncommon circumstances metastasectomy is not undertaken with palliative intent. The commonest cancer for which pulmonary metastasectomy is performed is colorectal cancer and in a systematic review[1] and in registry data.[2] R0 versus R1 resection has been shown to be associated with longer survival. Given that background information, surgeons naturally should strive for complete (R0) resection.

In a survey of practice, which revealed considerable variation, 74% of surgeon rated predictable failure to achieve complete resections as an absolute contraindication to pulmonary metastasectomy. A further 24% regarded it as a relative contraindication leaving only 2% who did not regard this as an obstacle.[3]

In clinical practice, when a patient with cancer develops lung metastasis the first question that occurs may well be "how long will I survive". There is a survival difference between those who have R0 resection and those who have residual disease after metastasectomy, and because surgery is offered with a prospect of cure, it seems obvious to think that extended resection should play an important role in achieving long-term survival in this unfortunate group of patients. Does it succeed in that objective? In the absence of conclusive evidence (which would be provided in an ideal world by a randomized trial), it is possible that apparent longer survival is product of case selection rather than surgical eradication.[4] Nevertheless, the practice of pulmonary metastasectomy is widespread,[3] and in many countries it is increasing.

There is a paradox to be considered in introducing this subject. In follow-up studies with sufficient cases of both types, a formal anatomic resection (such as lobectomy) is associated with lower 5-year survival rates than wedge resec-

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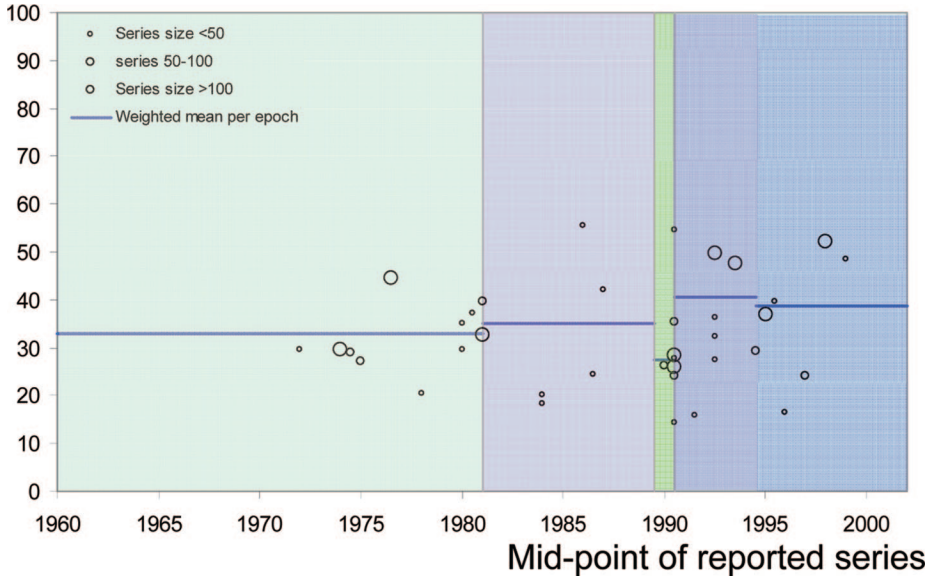


**FIGURE 1.** Percentage of patients with multiple metastases. (Adapted from *J R Soc Med.*[20])

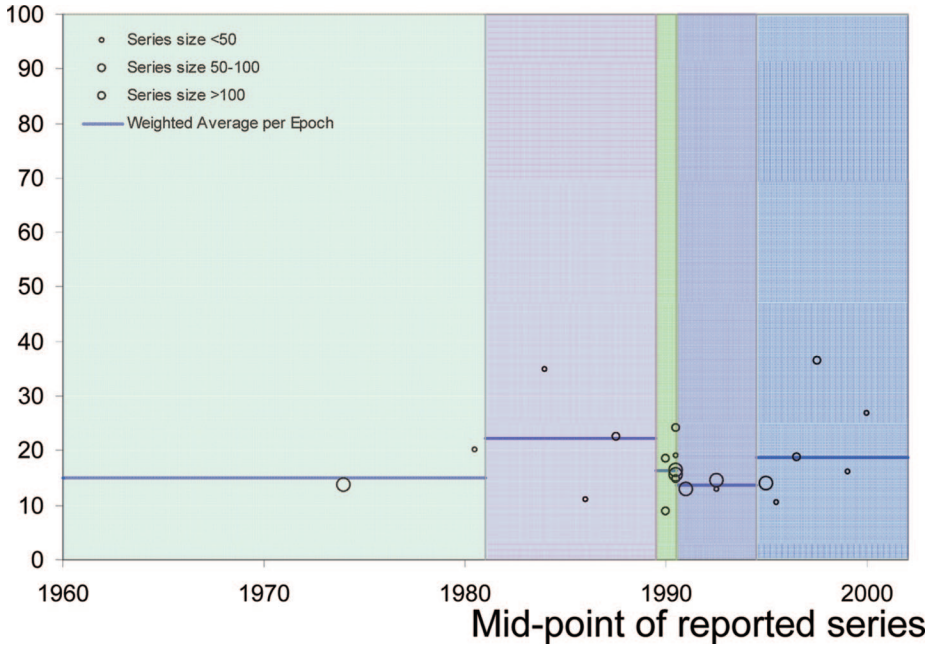


**FIGURE 2.** Percentage of patients having repeat pulmonary metastasectomy. (Adapted from *J R Soc Med.*[20])

tions (25% versus 39%) so more is not better in this instance.[1] In clinical practice, limited resection when possible to preserve lung parenchyma is nowadays the preferred method to perform metastasectomy. Nevertheless, we have noted that the role of extended resection for pulmonary metastasectomy is still unclear, and very poor information is available in the English literature on the extent of resection for lung metastasis. The purpose of this review is to explore the issues to help inform surgical practice.

## DEFINITIONS

For the purposes of this article, we consider "extended resection" to be an operation beyond the usual limits of commonplace practice, which is to perform local nonanatomic resection, of one, two, or three metastases, on one occasion.

- In the context of pulmonary metastasectomy, we will consider radical anatomic resection, specifically pneumonectomy, to be extended resection.
- We know from large numbers of case series that resection of one to three metastases is by far the commonest surgery and most patients with colorectal cancer have just one metastasis removed (Figure 1). So resection of say more than three, whether by multiple wedges or by precision techniques can also be considered for the purposes of this analysis, as in the realm of extended resection.

- Repeated operations can also be considered as extending the practice of pulmonary metastasectomy (Figure 2). One should note that for the purposes of the registry, Pastorino[5] allowed planned sequential thoracotomy to remove bilateral mestastasectomy as a single metastasectomy episode.

## METHODS

The basic evidence-based analysis was designed to evaluate the role of extended surgery in the treatment of lung metastasis. For this analysis, the following three research questions were formulated:

1. Q1 Is pneumonectomy indicated?
2. Q2 What are the actual criteria and limitations for the number of repeated resections?
3. Q3 What is the number of multiple resection justified in a single procedure?

In this article, we address these three in turn.

### Literature Search Criteria

A MEDLINE search of English language articles was conducted using simple key words that included for Q1, metastasectomy and pneumonectomy; for Q2, lung or pulmonary and repeated and metastasectomy; and for Q3, metastasectomy and multiple resection. Criteria for exclusion were review articles, manuscripts which did not reported series of more than five patients, or insufficient outcome data to be useful.

## RESULTS

### Q1 Is Pneumonectomy Indicated?

Pneumonectomy entails removal of the whole of one lung. Every pneumonectomy is associated with major physiological changes and any substantial reported series includes deaths and serious complications. It is probably a fair starting point that pneumonectomy has therefore only been performed for metastatic cancer if there are compelling reasons in that the cancer seems to be otherwise eradicated and the patient is very fit. The technical indications to resort to pneumonectomy to treat lung metastasis are typically for a very large metastasis or a metastasis critically involving hilar structure such that the surgeon cannot clear the cancer and leave a viable lung. There is therefore an inherent (a clinically appropriate) bias in the selection of cases entering any data set.

Very few series concerning primary or completion pneumonectomy were found. We were left with seven for consideration, six of which are in the Table 1,[2,6–10] one of them used twice for primary and completion pneumonectomy.

We found two reports of experience with pneumonectomy performed specifically for lung metastasectomy.[2,6] Most reports of pneumonectomy for lung metastasis are case reports or within a large experience of lung metastasectomy, and generally little information is available on long-term survival. Most patients do not survive more than 2 years and the best reported 5-year survival data are in the International Registry of Lung Metastases (IRLM) data.[2]

Completion pneumonectomy implicitly represents an operation performed as a last chance of cure from lung metastasis when previous lung metastasectomy has already been performed. The indications for completion pneumonectomy are the presence of a single central lesion or absence of enough lung tissue to obtain a free resection margin after one or more previous operation for lung metastasis. The reports are heterogeneous, some from (IRLM) data[2] and some from a series of completion pneumonectomy operations for a mixture of benign and malignant indications.[10]

It has been claimed in IRLM data that there is a better long-term survival after completion pneumonectomy for lung metastasis than primary pneumonectomy.[2] This conclusion cannot really be drawn from our evidence table. There are too few cases, and the difference is not striking. There are probably two factors involved in creating this impression. One is the degree of fitness that would be required to put a patient forward for this surgery. The other is the survivor selection: the patient has survived long enough after the primary and after the first metastasectomy to be in a favorable

**TABLE 1.** Evidence Table Showing Mortality and 5-yr Survival in Patients Undergoing Pneumonectomy or Completition Pneumonectomy for Lung Metastasis

| Authors | Date Range | No. of Patients | Mortality (%) | Outcome 5-yr Survival (%) |
|---|---|---|---|---|
| Primary pneumonectomy | | | | |
| Spaggiari et al.[6] | 1985–1995 | 42[a] | 7 | 17 |
| Koong et al.[7] | 1962–1994 | R0 112; R1 21 | 4; 19 | 23 |
| Completion pneumonectomy | | | | |
| Putnam et al.[8] | 1981–1992 | 19 | 11 | 25 |
| Grunenwald et al.[9] | 1985–1995 | 12 | 8 | 10 |
| Koong et al.[7] | 1962–1994 | 38 | 3 | 30 |
| Jungraithmayr et al.[10] | 1986–2003 | 9 | 0 | [b] |
| Chataigner et al.[11] | 1996–2005 | 11 | 0 | 41 |

[a] The data include primary pneumonectomy, completion pneumonectomy, and contralateral pneumonectomy for recurrence after metastasectomy.

[b] The data given imply that none have so far survived 5 yr. There was one recurrence free survivor 9 mo after surgery at the time of writing.

biologic group. Only patients with unusually indolent cancers will represent as candidates and remain under consideration for metastasectomy after the rigorous work up required in such unusual circumstances.

Anecdotally reported pneumonectomy results include publication bias (people are less likely to report their most disappointing outcomes). Consequently, the data reported are not predictive of what might be the outcome in future patients and this caveat should be born in mind if pneumonectomy were to be offered more liberally. On the basis of such information, Pairolero commenting on Spaggiari et al.[6] suggested that pneumonectomy for lung metastasis should, with specific exceptions, be avoided.

## Q2 Criteria for and Number of Repeated Resections

Recurrence of lung metastasis is not uncommon, and repeated resections are undertaken in an attempt to control the disease. In the clinical practice of a thoracic surgeon, it is not unusual that patients who experiences recurrent resectable lung metastases, and are found to remain free of disease at the primary location, are likely to be sent back to the thoracic surgeon for further surgery. There are plentiful accounts of patients who remain well for some time, or indefinitely after a second or subsequent reoperation for metastasectomy. Therefore, the question of how many repeated resection should be performed to achieve long-term survival is concrete, but still with some controversy.

Twenty-two publications have been found, of those 19 have been excluded on the basis of the title or the abstract. That left seven articles and, two more articles have been added from other resources (Table 2).

Multiple repeat resections are predominately used in sarcoma and colorectal surgery and tend to be reported in series of younger patients.

In patients with sarcoma, after repeated metastasectomy, the 3-year actuarial survival rate was 31%, and repeated resection was found to be an independent prognostic factor for survival.[11] In addition, Tronc et al. in pediatric patients with sarcoma suggest that repeat metastasectomy can salvage a subset of patients who retain favorable prognostic determinants: namely apparent complete resection was achieved and that there were few metastases to resect.[12] Temeck et al.[13] found a difference in median survival for resectable versus unresectable metastasis after a second, third, and fourth thoracotomy (5.6 versus 0.7 years, 5.2 versus 2.5 years, 2.2 versus 0.2 years, respectively). There was also a negative influence on survival associated with the number of preoperative nodules. The presence of two or more metastases in a recurrent case was associated with a poor survival of 20% at 5 years versus 60% if only one recurrent metastasis was present.[13] This finding is important because recurrent multiple metastasis is associated with poor long-term survival; "extended" operation should not be advocated in this unfortunate subgroup of patients.

Patients who are persistently free of disease at the primary location but who have recurrent, resectable metastatic disease of the lung are considered likely to benefit from operation a second, third, or even fourth time.[14] The first two metastasectomies more than 40 months (imprecisely referred to by the authors as the disease-free interval (DFI) is associated with significantly longer survival, $P = 0.0012$). On the other hand, a DFI less than 6 months between the first two metastasectomies is associated with negative prognosis and should therefore limit the promptness of surgical resection.

Another important point to clarify is the circumstance when the recurrent metastasis develops in the controlateral lung; there is no evidence that there is a difference in prognosis between recurrent metastases in the operated lung compared with the contralateral side.

Patients with osteosarcoma persistently free of primary osteosarcoma who developed recurrent resectable metastatic disease of the lung have similar DFI curves at 5 years. Park et al.[15] found that of the 10 patients who received a third metastasectomy, overall survival was 78% at 5 years after last operation, and Jaklitsch et al.[16]found that that where there had been multiple attempts to re-establish intrathoracic control of metastatic disease, the magnitude of benefit decays with each subsequent attempt.

## Q3 Number of Metastases Resected in a Single Procedure

It is not uncommon that more than 40 metastasis have been removed in a single procedure in patients with sarcoma.

Biology of the tumor and the presence of resectable metastatic disease confined to the lungs must be taken in

**TABLE 2.** Evidence Table Showing 5-yr Survival After Repeated Operations for Lung Metastases

| Author | Dates of Series | No. of Patients | Pathology | 5-yr Survival |
|---|---|---|---|---|
| Temeck et al.[13] | 1965–1995 | 70 | Sarcoma | 52[a] |
| IRLM, Pastorino[5] | 1945–1995 | Not stated | Mixed | 44 |
| Kandioler et al.[14] | 1973–1993 | 330 | Mixed | 48 |
| Jaklitsch et al.[16] | 1988–1998 | 54 | Mixed | 57 |
| Liebl et al.[21] | 1990–2005 | 42 | Sarcoma | 40.5 |
| Welter et al.[22] | 1993–2003 | 33 | Colorectal | 53.8 |
| Tronc et al.[12] | 1995–2006 | 25 | Paediatric | 25 |
| Park et al.[15] | 1995–2007 | 10 | Colorectal | 75 |
| Chen et al.[11] | 1989–2007 | 14 | Sarcoma | 19 |

References for Table 2 are not cited in the metastases. Liebl et al. and Welter et al.[21,22]
[a] Data taken from the Kaplan Meier survival curve.

account when multiple metastases are present. In patients with resectable lung metastases from sarcoma it is argued that "in patients with resectable pulmonary metastases from sarcoma or carcinoma, the number of metastases should have little influence on the surgical decision, except for delaying this decision in patients with several metastases until a significant interval, with or without treatment, has shown that metastatic disease remains resectable and confined to the lungs."[17]

Precision laser technique has been used to remove multiple lung metastases.[18] Rolle et al. after removing 3267 nodules in 328 patients with a mean of 10 nodules/patient reported a 5-year survival of 28% for 10 metastases removed and 26% for 20 or more metastases. But note, none of 44 patients with three or more lung metastases of colorectal cancer and DFI less than 1 year was cured from the operation,[19] and surgery when metastases are both recurrent and multiple is associated with poor long-term survival.[13] The claims for benefit for resection of larger numbers of metastases are within retrospective studies in which most patients have few metastases. Those operated on with many multiple metastases will have a range of other factors considered, which are likely to have been more favorable than average to allow them to have been selected for surgery. Multivariate analysis will probably not have made a complete statistical adjustment.

## COMMENT AND SUMMARY

Making evidence-based recommendations for extended treatment of lung metastasis is challenging for a number of reasons. The cases are usually a minority within the total patients in the follow-up study. Meta-analysis is not possible due to the insufficient quality of the available literature.

It is clear that the decision to perform an extended metastasectomy it is not just a demonstration of surgical ability but has other clinical motives. The aspiration of the surgeon to achieve long-term survival for patients remains the most significant. To accomplish this objective, several factors must be taken in consideration such as histology and biology of the tumor, DFI, number, size and position of the metastases, laterality, and recurrence. A combination of these factors is sometimes of great importance, in fact for instance multiple recurrent lung metastases are associated with poor long term survival and therefore extended surgery should be discouraged.

The choice of nonanatomic (laser precision technique or wedge resection) versus anatomic resection (segmentectomy, lobectomy, and pneumonectomy) depends on the patient's lung function, position, number, size, and position of the metastases. As the evidence supporting pneumonectomy is poor, a surgeon before undertaking pneumonectomy or completion pneumonectomy for lung metastasis should have a frank and detailed discussion with the patient and relatives.

Q1 Extended resection for pulmonary metastasis is feasible and may be justified in individualized circumstances. We believe caution is warranted before performing pneumonectomy because it is debatable whether any possible benefit justifies the adverse consequences of this surgery and long term survival is poor.

Recurrent metastasectomy poses recurrent difficulties in decision making. An aggressive approach to pulmonary metastases of sarcomas is justified by experts as repeated resections have demonstrated prolonged survival. Recurrent metastasectomy is not advocated in presence of multiple lung nodules and the magnitude of benefit decays with each subsequent attempt.

Q2 Multiple attempts to re-establish intrathoracic control of metastatic disease is supported by some authors in carefully selected patients, but apparent benefit may be a result of survivor bias and the ratio of harm to benefit is likely to increase with each subsequent attempt.

If multiple lung metastases are to be removed no matter what their number, consideration should be given to the histology and the biologic behavior of the tumor, the DFI, and the quantity lung tissue which will be lost.

Q3 If on accepted criteria specific to the primary cancer the patient is a candidate for pulmonary metastastasecomy, then the goal should be to resect all metastases that are there, irrespective of the number. However, with increasing pulmonary metastatic count there is less good survival and greater loss of lung tissue. These issues should be fully considered at the planning stage.

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