

# Pulmonary metastasectomy: a cross sectional survey

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**Background:** No prospective randomised studies or international guidelines exist for conduct of pulmonary metastasectomy. The aim of this study was to generate general recommendations for the practice of pulmonary metastasectomy through a cross sectional survey of thoracic surgeons.

**Methods:** A panel of international experts who participated in a consensus statement formation on video-assisted thoracoscopic surgery (VATS) lobectomy were approached to participate in the survey. The Delphi methodology consisting of two rounds of voting was used to establish recommendations. Clinical practice was deemed 'recommended' if 50–74% of the experts reached agreement and 'highly recommended' if 75% or more of the experts reached agreement following the second round of voting.

**Results:** Twenty-two experts from 8 countries completed both rounds of standardised questionnaires. Recommendations were reached on all of the 18 questions concerning the role, indications, contraindications, preoperative evaluation, operative strategy, follow-up and alternative treatment strategies for pulmonary metastasectomy.

**Conclusions:** The results of this survey represent a collective agreement among international thoracic surgery experts and establishes general recommendations for the practice of pulmonary metastasectomy.

**Keywords:** Pulmonary metastasectomy; lung resection

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## Introduction

In the current era of evidence driven surgical practice, pulmonary metastasectomy is supported only by non-randomised, retrospective case series and metastasectomy registries. Despite its widespread conduct, there are no published clinical guidelines for pulmonary metastasectomy. The goals of this research were to identify important and controversial topics in contemporary pulmonary metastasectomy and conduct an international survey to generate general guidelines for the practice of pulmonary metastasectomy.

The first published case-report of pulmonary metastasectomy was performed in 1939 (1). Since that time,

the understanding of cancer biology including patterns of cancer spread, imaging, surgical techniques and adjunctive therapies has broadened immensely. The original resection criteria put forward by Thomford in 1965, emphasised the role of pulmonary metastasectomy to primarily improve survival, whilst also being used palliatively for patients with locally complicated disease (2). Rusch in 1995 described her own set of criteria for pulmonary metastasectomy. These included control of the primary tumour, patient anatomy, physiology and pulmonary reserve sufficient to withstand planned resection, complete metastatic resection, absence of extra-thoracic disease, and surgical therapy when no less morbid, equally effective alternative systemic therapy is

available. Rusch's principles have generally been accepted by many thoracic surgeons internationally over the last two decades (3).

Following on from Thomford and Rusch, and the multitude of retrospective studies that have been published on pulmonary metastasectomy, in 2005 the European Society of Thoracic Surgeons (ESTS) formed a working group and distributed a questionnaire in 2006, surveying surgeons with regards to their current surgical approaches to pulmonary metastasectomy (4). It provided an insight into the patterns of pulmonary metastasectomy across a wide range of clinical practices.

## Methods

### *Questionnaire development*

An online literature search was used to identify important and controversial topics in contemporary pulmonary metastasectomy. These topics included the role of surgery, indications and contra-indications to resection, pre-operative patient evaluation, operative strategies, follow up and alternative treatment. The questions were designed in such a way as to lead respondents to give general recommendations.

### *Invitation to participate*

The international experts approached to participate in this study were a pre-formed group of thoracic surgeons who previously contributed to a consensus statement on video-assisted thoracoscopic surgery (VATS) lobectomy (5). They were identified originally in 2012 as representatives of international thoracic units who had completed more than 100 VATS lobectomy procedures. No incentives or disincentives were suggested as part of their participation or non-participation.

### *Voting process*

An individualised invitation was emailed to each of experts with a link to a secure website that presented 18 questions. Two rounds of voting were used to strengthen validity. Invitation to the first round of voting was distributed in September 2017. Two reminder e-mails were sent to experts before the first round of voting was closed. An e-mail invitation to view results of the first round of voting and concurrently participate in the second round of voting was distributed in November 2017 and two reminder e-mails

subsequently sent. The results from the second round of voting formed the basis for practice recommendations.

### *Ethics*

There was no direct patient contact or review of confidential information required for this study. Ethics committee approval was deemed not required.

## Results

### *Demographic data*

Twenty-five international experts from 9 countries completed the first round questionnaire. Twenty-two of these 25 completed the second round questionnaire. Of the respondents who completed the second round questionnaire, 73% were from Europe, 23% were from North America and 4% from Australia.

### *Recommendations*

The survey questions and details of their responses is presented in *Table 1*. A summary of recommendations for each of the 18 consensus questions is presented in *Table 2*. Clinical practice was deemed 'recommended' if 50–74% of the experts reached agreement and 'highly recommended' if 75% or more of the experts reached agreement following the second round of voting. Consensus was reached on the following points: (I) the role of pulmonary metastasectomy is to improve local disease control (91%, 'highly recommended'); and improve survival (82%, 'highly recommended'); (II) favourable histological subtypes for pulmonary metastasectomy include colorectal carcinoma (100%, 'highly recommended'), osteosarcoma (95%, 'highly recommended'), soft tissue sarcoma (91%, 'highly recommended'), renal cell carcinoma (86%, 'highly recommended'), melanoma (68%, 'recommended'), head and neck carcinoma (68%, 'recommended'), and gynaecological (cervical/endometrial/ovarian) cancer (55%, 'recommended'); (III) primary tumour should be controlled prior to metastasectomy (100%, 'highly recommended'); (IV) both positron emission tomography (PET) and computerized tomography (CT) should be used in pre-operative imaging (82%, 'highly recommended'); (V) patients should be discussed in a multi-disciplinary meeting (100%, 'highly recommended'); (VI) tissue biopsy is not recommended prior to resection in patients with suspected pulmonary

**Table 1** Survey questions and responses

Question	Round 1: number of positive respondents [%]	Round 2: number of positive respondents [%]
What do you consider as the role of pulmonary metastasectomy?		
Improve local disease control	18 [72]	20 [91]
Improve survival	19 [76]	18 [82]
Improve quality of life	10 [40]	3 [14]
None of the above	0 [0]	0 [0]
What histological subtypes do you consider favourable for pulmonary metastasectomy?		
Colorectal carcinoma	25 [100]	22 [100]
Breast carcinoma	6 [24]	5 [23]
Head and neck carcinoma	13 [52]	15 [68]
Renal cell carcinoma	22 [88]	19 [86]
Soft tissue sarcoma	21 [84]	20 [91]
Osteosarcoma	23 [93]	21 [95]
Melanoma	12 [48]	15 [68]
Gastric carcinoma	4 [16]	4 [18]
Gynecological (cervical/endometrial/ovarian) cancer	12 [48]	12 [55]
None of the above	0 [0]	0 [0]
Would you generally recommend that the primary tumour be controlled prior to pulmonary metastasectomy?		
Yes	25 [100]	22 [100]
No	0 [0]	0 [0]
What pre-operative imaging would you recommend prior to pulmonary metastasectomy?		
CT chest	3 [12]	4 [18]
PET	0 [0]	0 [0]
Both CT and PET	22 [88]	18 [82]
In patients with pulmonary metastasis would you generally recommend local and systemic treatment strategies be discussed in a multidisciplinary meeting prior to resection?		
Yes	25 [100]	22 [100]
No	0 [0]	0 [0]
Would you generally recommend tissue biopsy prior to resection for a patient with suspected pulmonary metastasis?		
Yes	3 [12]	2 [9]
No	20 [80]	19 [86]
Not sure	2 [8]	1 [5]
Would you generally consider incomplete metastasectomy a contraindication to surgery?		
Yes	22 [88]	20 [91]
No	2 [8]	2 [9]
Not sure	1 [4]	0 [0]

**Table 1** (continued)

Table 1 (continued)

Question	Round 1: number of positive respondents [%]	Round 2: number of positive respondents [%]
Would you generally recommend preoperative lymph node assessment for enlarged (>10 mm) or glucose avid lymph nodes?		
Yes	16 [64]	16 [73]
No	8 [32]	5 [23]
Not sure	1 [4]	1 [5]
In patients with progressive disease would you generally recommend a period of observation prior to resection?		
Yes	20 [80]	21 [95]
No	4 [16]	1 [5]
Not sure	1 [4]	0 [0]
Please rank the priority of your goals of treatment for pulmonary metastasectomy		
Complete resection [a]	abc 16+ acb 3=19 [76]	abc 18 + acb 0=18 [82]
Preservation of lung function [b]	bac 4 + bca 0=4 [16]	bac 4 + bca 0=4 [18]
Minimisation of surgical invasiveness [c]	cba 0 + cab 2=2 [8]	cba 0 + cab 0=0 [0]
What would you recommend as the preferred approach to pulmonary metastasectomy?		
VATS	22 [88]	18 [82]
Thoracotomy	3 [12]	2 [9]
Robotic	0 [0]	1 [5]
Laser	0 [0]	1 [5]
If performing pulmonary metastasectomy via minimally invasive techniques, how do you recommend metastatic lesions be identified?		
Visualisation and pre-operative imaging correlation	22 [88]	19 [86]
Instrument palpation	15 [60]	11 [50]
Manual palpation	19 [76]	19 [86]
Pre-operative hook-wire localisation	4 [16]	4 [18]
Immunofluorescent/dye localisation	3 [12]	4 [18]
None of the above	1 [4]	0 [0]
In which situations would you recommend thoracotomy for pulmonary metastasectomy?		
Multiple lesions	16 [64]	14 [64]
Large lesion size	10 [40]	8 [36]
Central lesion location	11 [44]	9 [41]
Preservation of lung function	12 [48]	12 [55]
None of the above	2 [8]	1 [5]

Table 1 (continued)

Table 1 (continued)

Question	Round 1: number of positive respondents [%]	Round 2: number of positive respondents [%]
What extent of surgical resection do you consider reasonable for pulmonary metastasectomy?		
Sub-lobar (wedge) resection	23 [92]	22 [100]
Segmentectomy	23 [92]	21 [95]
Lobectomy	24 [96]	21 [95]
Bilobectomy	11 [44]	14 [64]
Pneumonectomy	2 [8]	2 [9]
None of the above	0 [0]	0 [0]
Would you generally recommend intra-operative lymph node assessment?		
Yes	15 [60]	11 [50]
No	7 [28]	10 [45]
Not sure	3 [12]	1 [5]
Following metastectomy, at what time intervals would you recommend repeat chest CT or PET?		
3 months	12 [48]	9 [41]
6 months	16 [64]	15 [68]
12 months	5 [20]	3 [14]
2 years	4 [16]	3 [14]
Beyond 2 years	4 [16]	3 [14]
None of the above	0 [0]	0 [0]
Would you generally recommend re-do metastasectomy for pulmonary metastases?		
Yes	20 [80]	22 [100]
No	1 [4]	0 [0]
Not sure	4 [16]	0 [0]
What would you generally recommend as alternative loco-regional treatment to surgery?		
Radiofrequency ablation	15 [60]	14 [64]
Stereotactic radiotherapy	24 [96]	22 [100]
Cryoablation	5 [20]	5 [23]
Microwave ablation	8 [32]	9 [41]
None of the above	0 [0]	0 [0]

CT, computed tomography; PET, positron emission tomography.

metastases (86%, 'highly recommended'); (VII) incomplete metastasectomy is a contraindication to surgery (91%, 'highly recommended'); (VIII) enlarged (>10 mm) or glucose avid lymph nodes should be assessed prior to metastasectomy (73%, 'recommended'); (IX) patients with progressive disease should be observed prior to metastasectomy (95%,

'highly recommended'); (X) complete resection is the primary treatment goal (82%, 'highly recommended'); (XI) VATS is the preferred operative approach (82%, 'highly recommended'); (XII) metastatic lesions should be identified intra-operatively by visualisation and pre-operative imaging correlation (86%, 'highly recommended'), manual palpation

**Table 2** Summary of recommendations

Recommendation	Level of recommendation
Role of pulmonary metastasectomy	
Improve local disease control	Highly recommended
Improve survival	Highly recommended
Favourable histological subtypes for metastasectomy	
Colorectal carcinoma	Highly recommended*
Osteosarcoma	Highly recommended
Soft tissue sarcoma	Highly recommended
Renal cell carcinoma	Highly recommended
Head and neck carcinoma	Recommended
Gynecological (cervical/endometrial/ovarian) cancer	Recommended
Primary tumour control prior to metastasectomy	Highly recommended*
Both CT and PET imaging prior to metastasectomy	Highly recommended
Multidisciplinary team meeting discussion prior to metastasectomy	Highly recommended*
Tissue biopsy of suspected metastatic lesion not required	Highly recommended
Incomplete metastasectomy is a contraindication	Highly recommended
Enlarged (>10 mm) or glucose avid lymph nodes should be assessed prior to metastasectomy	Recommended
Patients with progressive disease should be observed prior to metastasectomy	Highly recommended
The primary treatment goal is complete resection	Highly recommended
VATS is the preferred operative approach	Highly recommended
Metastatic lesions should be identified intra-operatively by	
Visualisation and pre-operative imaging correlation	Highly recommended
Manual palpation	Highly recommended
Instrument palpation	Recommended
Thoracotomy is preferred for	
Multiple lesions	Recommended
Preservation of lung function	Recommended

**Table 2** (continued)**Table 2** (continued)

Recommendation	Level of recommendation
Extent of reasonable surgical resection	
Wedge resection	Highly recommended*
Segmentectomy	Highly recommended
Lobectomy	Highly recommended
Bilobectomy	Recommended
Lymph nodes should be assessed intra-operatively	Recommended
A repeat CT chest or PET should be performed at 6 months post resection	Recommended
Re-do metastasectomy is indicated if further pulmonary metastases develop	Highly recommended*
Alternative loco-regional treatments include	
Stereotactic radiotherapy	Highly recommended*
Radiofrequency ablation	Recommended

\*, indicates unanimous agreement. CT, computerized tomography; PET, positron emission tomography.

(86%, 'highly recommended') and instrument palpation (50%, 'recommended'); (XIII) thoracotomy is preferred for multiple lesions (64%, 'recommended') and preservation of lung function (55%, 'recommended'); (XIV) Acceptable extent of resection is wedge resection (100%, 'highly recommended'), segmentectomy (95%, 'highly recommended'), lobectomy (95%, 'highly recommended') and bilobectomy (64%, 'recommended'); (XV) lymph nodes should be assessed intra-operatively (50%, 'recommended'); (XVI) repeat CT-chest or PET should be performed 6 months following resection (68%, 'recommended'); (XVII) re-do metastasectomy is indicated in recurrent disease (100%, 'highly recommended'); (XVIII) Alternative loco-regional treatments include stereotactic radiotherapy (100%, 'highly recommended') and radiofrequency ablation (64%, 'recommended').

## Discussion

### General principles of pulmonary metastasectomy

The role and conduct of pulmonary metastasectomy in

contemporary surgical practice remains controversial. Larger clinical series suggest that metastatic tumour resection improves survival (6). In particular, survival benefit is best seen in the context of oligometastatic disease where metastases are completely resected and there is a long disease-free interval from diagnosis of the primary tumour (7). Respondents here agreed that pulmonary metastasectomy is used to improve survival as well as improve local disease control in the context of primary tumour control. Further, complete resection was considered of paramount importance with incomplete resection a contraindication to surgery. Sparing pulmonary parenchyma and limiting surgical invasiveness were considered lesser priorities. It was also agreed that patients with progressive disease be observed prior to metastasectomy, consistent with data suggesting poorer survival in these patients undergoing early resection (8). Tissue biopsy was not generally recommended in the case of suspected metastatic disease.

#### *Histological subtype favourability*

Pulmonary metastasectomy represents a potentially curative treatment for patients with metastatic sarcoma, however its role in other histological subtypes is less clear (7,9,10). Interestingly, despite a previous survey of surgeons in Britain and Ireland suggesting equipoise for the resection of colorectal metastases and a randomised control trial currently enrolling patients with colorectal cancer to undergo or not undergo pulmonary metastasectomy, it was unanimously agreed here that colorectal carcinoma is a favourable histological subtype for metastasectomy (11,12). In addition to sarcoma and colorectal carcinoma, renal cell carcinoma, melanoma, gynaecological cancer, and head and neck carcinomas were also considered favourable to resection despite less favourable evidence for the latter (13). Certainly, there is now less favouritism to resect metastatic breast cancer from the lung. This is most likely due to improving systemic therapies effective at prolonging life in the disease (14).

Discussion of patients in a multidisciplinary setting was also unanimously recommended. Multidisciplinary team management has shown to be advantageous in many clinical specialties (15). It affords the opportunity to discuss complimentary and alternate systemic and loco-regional disease control strategies. Targeted, ablative therapies to metastatic pulmonary lesions have increasingly been used instead of surgery and here the preference for stereotactic radiotherapy was again emphasised (16).

#### *Imaging*

The quality and application of imaging for metastatic pulmonary disease continues to improve. Computed tomography (CT) of the chest in combination with positron emission tomography (PET) scanning play complimentary roles in identifying the number, location, size and character of pulmonary masses as well as assessment of extra thoracic disease (17,18). The information obtained from these imaging modalities often determines operability and extent of resection. PET has shown to be particularly sensitive in assessment of lesions >10 mm and potentially modifies treatment plans when extra-thoracic disease is discovered (19). The limitations of CT scanning, particularly in missing small malignant nodules has been recognised but likely to be reduced as imaging resolution improves (20). It is perhaps unsurprising that use of both imaging modalities is highly recommended by the expert panel in patients being considered for pulmonary metastasectomy. The role of re-imaging post metastasectomy has not been clearly defined and often longer term follow up is conducted by non-surgical members of the multidisciplinary team (4). Notwithstanding this, following up patients with repeat chest CT at 6 months post resection was recommended by expert consensus of surgeons.

#### *Lymph node assessment*

Hilar and mediastinal lymph node involvement is a poor prognostic indicator in pulmonary metastatic disease (21). Despite this, systematic assessment of lymph nodes has historically not been widespread (4) and it is controversial whether patients with positive nodes should be excluded from pulmonary metastasectomy (22). Both preoperative tissue assessment of radiologically suspicious lymph nodes and intra-operative lymph node assessment is 'recommended' by the expert panel. Whether nodal positivity would change the management of patients was not determined in the questionnaire.

#### *Operative strategy*

Numerous studies have suggested the benefit of less invasive approaches to lung resection in the context of primary lung cancer (23-26). Specifically, VATS has shown to be potentially curative, less painful and expeditious of recovery compared with traditional thoracotomy (27).

With advancement of modern thoracoscopic technology and increasingly advanced VATS skills sets, VATS is the favoured approach for pulmonary metastasectomy in this study. The majority support for the approach is contrasted to the 40% support given to VATS as the preferred technique in 2008 (4). Given the panel of experts were original contributors to a consensus statement on VATS lobectomy, it is not surprising that VATS was favoured, although agreement was not unanimous and thoracotomy was considered indicated in the presence of multiple metastatic lesions and for the preservation of lung function.

Lesion localisation in the VATS approach is dependent on a combination of pre-operative imaging and intra-operative palpation. Newer technologies including dye and hook-wire localisation were not recommended in this study. VATS has often been criticised for missing occult metastases and minimising surgical margin compared with thoracotomy (20,28,29). Despite this, numerous authors have shown no difference in operative survival, disease free interval or ipsilateral recurrence between VATS and open approaches (30,31).

The extent of resection, in particular the limit of reasonable resection, has often been discussed. Here the general recommendation to resect lung parenchyma to achieve negative margins up to and including lobectomy was 'highly recommended' and up to bilobectomy 'recommended'. With the increasing sophistication of lung stapler technology, the resection of multiple lesions with minimisation of alveolar air leak has been simplified. The approach to confirmed or suspected bilateral disease was not investigated here.

Re-do pulmonary metastasectomy is sometimes required, particularly for young patients with osteogenic and soft tissue sarcomas where surgery is the preferred disease control strategy (7). With the development of new pulmonary metastases following initial resection, it is 'highly recommended' here that patients are considered for further surgery. In the case of ipsilateral chest re-entry, the operative strategy may be different to first time entry. Specifically, minimally invasive approaches may be less appropriate given the presence of pleural adhesions, obscured tissue planes or multiple lesions.

### **Study limitations**

This study has been designed to create a list of general recommendations formulated by an international panel of

experts. The expert panel consisting of surgeons previously formed as part of a primary lung cancer VATS lobectomy consensus group. These surgeons are likely to have a more advanced thoracoscopic skill set and the VATS approach to metastasectomy may have been emphasised.

### **Conclusions**

This cross sectional survey establishes general recommendations for the practice of pulmonary metastasectomy. The recommendations are likely to be widely applicable to many clinical circumstances though not intended to replace patient specific cancer care. It is anticipated that it will influence and potentially shape contemporary clinical practice guidelines.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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