The role and benefit of minimally invasive repeat pulmonary metastasectomy: a narrative review

Narendran Balasubbiah[1,2]^, Padungkiat Tangpiroontham[2]^

[1]Kuala Lumpur General Hospital, Jalan Pahang, Kuala Lumpur, Malaysia; [2]Lung and Thoracic Cancer Center, Department of Cardiothoracic Surgery, Bangkok Hospital, Bangkok, Thailand

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Correspondence to: Padungkiat Tangpiroontham, MD. Department of Cardiothoracic Surgery, Bangkok Hospital, 2 Soi Phetchaburi 47 Yaek 10, Bang Kapi, Huai Khwang, Bangkok 10310, Thailand. Email: dr.padungkiat@gmail.com.

Background and Objective: Redo or repeat pulmonary metastasectomy (RPM) is the removal of metastatic lung nodules for the second or more times from the same lung. After the first pulmonary metastasectomy (PM), 50% patients get a recurrence. RPM has been gaining popularity due to encouraging results in survival and surgical outcomes. There are no proper guidelines for RPM due to weakness in the level of evidence and, this is a narrative review of minimally invasive surgery and its benefits and role in RPM.

Methods: Electronic database search was done in PubMed and Google Scholar on 31 December 2022. Combinations of research Medical Subject Headings and search terms were keyed in. The search terms were 'redo or repeat' and 'pulmonary', and 'metastasectomy', and 'minimally invasive surgery'. Out of 550 manuscripts, only five reports were obtained for surgical approach mentioning minimal access surgery performed for PM and six for RPM.

Key Contents and Findings: Good survival benefits of RPM was seen across the records with acceptable post-operative morbidity and zero mortality, as long as patients are operable and resectable with adequate lung reserve. Comparison study between first PM and RPM showed no difference in complication rate. Type of primary tumor histology determines the survival and the recurrence outcomes. The common tumors subjected to RPM are colorectal cancer, sarcoma, urothelial carcinoma, renal cell carcinoma, head and neck cancers, hepatocellular carcinoma and germ cell tumors. Minimal invasive surgery (MIS) has made multiple resection possible with fewer adhesions allowing easier access to the pulmonary nodule for RPM with decreased complications. In cases where there are 3 nodules or more, bimanual palpation of the whole lung to detect nodules which was missed during preoperative radiological examinations can be overcome with hybrid video-assisted thoracoscopic surgery (VATS). Patients with bilateral pulmonary metastasis could also benefit from bilateral VATS or subxiphoid approach for gaining access to bilateral lung fields.

Conclusions: MIS along with thin slice CT scans could achieve an accurate metastasis detection for removal of repeated lung metastatic lesions in a safe and effective manner.

Keywords: Pulmonary metastases; repeat metastasectomy; video-assisted thoracoscopic surgery (VATS)

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^ ORCID: Narendran Balasubbiah, 0000-0002-9938-7721; Padungkiat Tangpiroontham, 0009-0000-7071-8462.

Introduction

Redo or repeat pulmonary metastasectomy (RPM) is the removal of metastatic lung nodules for the second or more times from the same lung. Pulmonary metastasectomy (PM) has been remarkably described since 1884 before proper anesthesia and sterility was practiced (1). RPM has been gaining popularity since the first published case studies for PM showed encouraging results. The 5 years survival rate in patients who underwent RPM was 58–79%, meanwhile only 24–52% survive if nodule is not removed (2-4). Tumor histology plays an important role in overall survival outcomes in PM (5). First series of PM was described by Alexander and Haight in 1947 (6). Revision to the selection criteria was done in 1965 by Thomford *et al.*, remaining relevant till today (7). The criteria are applicable for both PM and RPM which are, (I) primary tumor is controlled, (II) no extra thoracic lesions are present, with exception of hepatic and brain lesions which is resectable, (III) pulmonary metastases are technically resectable with tolerable general and functional risks. There are no proper guidelines for PM due to weakness in the level of evidence though The Society of Thoracic Surgeons attempted to clarify this pertinent question (8,9). There are no proper case series, randomized trials, or proper guidelines available for RPM. Only a few studies specifically focus on RPM and the available results are relatively limited in number within a larger study addressing PM (10). This is a narrative review of minimally invasive surgery and its benefits and role in RPM, and presented in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-23-32/rc).

Methods

Electronic database search was done in PubMed and Google Scholar on 31 December 2022, with no language restrictions. Combinations of research Medical Subject Headings (MeSH) and search terms were keyed in. The search terms were 'redo or repeat' and 'pulmonary', and 'metastasectomy', and 'minimally invasive surgery'. A total of 550 reports was retrieved. Two hundred reports were removed due to duplication and further 339 removed as not complying to the research question. Only five reports were obtained for surgical approach mentioning minimal access surgery performed for PM and six for RPM. *Table 1* shows the study method employed.

Discussion

Survival benefits of RPM

Mineo *et al.* noted patients who underwent RPM had a longer survival than patients who went for only one surgery. The 5-year survival was 65% and this was significantly higher than the value recorded for patients undergoing only one metastasectomy (42%; P=0.021). It was noted, the more number of times PM is repeated, the greater is the probability for recurrence and the less the disease free interval concluding more morbidity with higher number of resections (11).

International Registry of Lung Metastases reported survival was higher for RPM compared to only one PM operation after 5 and 10 years (44% *vs.* 39% and 29% *vs.* 25%, respectively) (12). Treasure *et al.*, in a systematic review of malignant sarcoma with 1,357 patients in 14 studies, 579 (43%) received RPM showed an increased survival outcome (13). In a Japanese study by Chen *et al.*, RPM for recurrent pulmonary metastasis showed a favorable overall survival (14). A multicenter study done in 46 centers in Japan, 898 PM was performed from year 2004 to 2008. One hundred and thirty-two out of 216 (61%) patients who developed recurrent pulmonary metastases underwent RPM for colorectal tumor metastasis. Their 5-year overall survival was 75.6%, concluding that resectable lung-limited recurrence of pulmonary metastasis could provide favorable survival outcome. In the Korean study by Park *et al.*, out of the 48 patients who underwent second PM, overall and disease-free survivals were 79% and 49% respectively. Out of the 10 patients who received a third metastasectomy, overall survival was 78% at 5 years post operation showing a similar survival benefit after the second and third PM (15). All these studies show good evidence for RPM to improve survival benefits in patients who are operable and fit to undergo resections (16). Treasure *et al.* discussed this phenomenon as 'survivability' characteristic of patients who could undergo multiple PM and have better survival outcomes. Randomizing treatment received for patients with recurrent pulmonary metastasis may be the only way to differentiate causation from association. There needs to be further research in the survivability characteristics of patients with regards to genomic characteristics for survival. *Table 2* shows the summary list of records available for RPM with survival benefit and disease-free interval.

Table 1 Search strategy summary

Items	Specifications
Date of search	31st December 2022
Database and other sources of search	PubMed and Google Scholar with no language restrictions
Search terms used for search strategy	'Redo or repeat' and 'pulmonary', and 'metastasectomy', and 'minimally invasive surgery' was typed in the search selection box
Timeframe	All publications up to 31st December 2022
Inclusion and exclusion criteria	All records on redo pulmonary metastasectomy and minimally invasive surgery. Exclusion criteria are primary lung tumors
Selection process	Selection of articles done by 2 Thoracic surgeons independently (550 articles); records after duplicates were removed (350 records); records were screened and incomplete articles removed (150 records); full texted articles were assessed for eligibility and removed with reasons (50 articles); studies included in final synthesis (11 articles)

Table 2 Studies for RPM

No	Study (reference)	No. of patients, n	No. of PM (no. of patients)	Survival rate 3 years, %	Survival rate for 5 years, %	Survival rate for 10 years, %	Cumulative overall survival, mean (months)	5-year DFS, %
1	Hishida *et al.* (16)	216	1 [137], 2–4 [66], >4 [13]	–	58.7	–	–	–
2	Chudgar *et al.* (17)	141	–	–	–	–	44.9	–
3	Mineo *et al.* (11)	113	2 [113], 3 [54], 4 [31], 5 [8], 6 [3]	–	65	–	–	–
4	Menna *et al.* (2)	92	92 [2], 11 [3]	80	60	–	30	–
5	Krüger *et al.* (18)	64	2 [64], 3 [35], 4 [12], 6 [5]	82.3	63.3	–	66 (median)	–
6	Sponholz *et al.* (4)	52	–	–	75	–	–	–
7	Park *et al.* (15)	48	2 [48], 3 [10]	–	79	–	42.8 (median)	–
8	Welter *et al.* (19)	33	–	–	53	20.6	72.6 (median)	–
9	Sakamoto *et al.* (20)	5	–	–	–	–	22	–
10	Mizuguchi *et al.* (21)	5	–	67	–	–	65	–
11	Han *et al.* (22)	2	–	-	–	–	10	37.5

RPM, redo or repeat pulmonary metastasectomy; PM, pulmonary metastasectomy; DFS, disease-free survival.

Perioperative morbidity, mortality and survival outcome for RPM

Reports has been scanty for perioperative morbidity. All the studies reported no postoperative deaths after first PM surgery. However, one study reported complications in 18 patients who underwent repeated surgeries done for pulmonary metastasis as per following; atrial fibrillation (n=17), lung infection (n=5), prolonged air leak (n=2), respiratory distress (n=1), bleeding requiring transfusions (n=2) and wound infection (n=1) (23). In Switzerland, 264 patients underwent PM, over a period of 15 years for various primary cancers. One hundred and ninety-three (73.1%) patients were operated by video-assisted thoracoscopic surgery (VATS) and 21 (26.9) by thoracotomy. Out of the 264 cases operated, 66 (25%) patients underwent RPM, some up to five times bringing the total number

Table 3 Study of primary tumor histology for RPM

No	Study (reference)	No. of patients	Type of primary histiocyte	Negative predictive factor for RPM
1	Hishida *et al.* (16)	216	CRC	Primary tumor in the rectum
2	Chudgar *et al.* (17)	141	Soft tissue sarcoma	Preoperative chemotherapy prior to RPM and Involved resection margin
3	Mineo *et al.* (11)	113	Not mentioned	Multiple lung metastases and short DFI prior to RPM
4	Menna *et al.* (2)	92	CRC	Positive nodal metastases
5	Kruger *et al.* (18)	64	CRC 19 (29.7%), renal cell carcinoma 15 (23.4), sarcoma 9 (14.1%), urothelial carcinoma 4 (6.3%), head and neck cancers 4 (6.3%), and others 13 (20.3%)	–
6	Sponholz *et al.* (4)	52	CRC	Lower grading of primary tumour and complete resection margin associated with better prognosis for RPM
7	Park *et al.* (15)	48	CRC	–
8	Welter *et al.* (19)	33	CRC	Number of lung metastases
9	Sakamoto *et al.* (20)	5	CRC	Higher pre operative CEA levels
10	Mizuguchi *et al.* (21)	5	CRC	–
11	Han *et al.* (22)	2	Urothelial carcinoma	–

RPM, redo or repeat pulmonary metastasectomy; CRC, colorectal carcinoma; DFI, disease-free interval; CEA, carcinoembryonic antigen.

to 116. Comparison between the 2 groups of patients who underwent first PM versus RPM revealed, the post-operative cardiopulmonary complication rate was the same at 12%. There were no readmissions nor reoperations in the RPM group. The only significant parameter was the median duration of drain being 2 days for RPM (24). The following studies show RPM is justifiable and further multiple metastasectomy is possible if the patients are operable and lung reserves permits. RPM resections can be safely carried out and provides long term survival in patients with recurrent pulmonary metastasis.

Role of RPM in various primary cancers

Literature review proved RPM to be beneficial in colorectal cancer, sarcoma, urothelial carcinoma, renal cell carcinoma, head and neck cancers, hepatocellular carcinoma and germ cell tumours. Surgical margin clearance (R0 resection) is mentioned by Chudgar *et al.* (17) and Sponholz *et al.* (4), as an important prognostic factor in terms of disease free interval and survival benefit (4,17).

The primary tumour which is most commonly operated in PM is colorectal carcinoma (25). Its histology has a good 5-year survival rates up to 68% (26). Preoperative carcinoembryonic antigen (CEA), extrathoracic metastatic lesions, age less than 70 years old and rectal location demonstrated poorer prognosis (27-29). The second most common primary tumour undergoing PM is renal cell carcinoma (30). For sarcomatous primary tumors, surgical excision gives the best treatment strategy for a cure with 15% to 51% 5-year survival rate (31-34). Negative prognostic factors are high grade tumour and bilateral lung involvement (33). In head and neck cancers with pulmonary metastases, adenoid cystic carcinoma has a better prognosis compared to squamous cell carcinoma (35). The type of primary tumor histology determines the survival outcome post RPM. *Table 3* is a summary of studies with histology of primary cancers.

Role of minimal invasive surgery (MIS)

MIS and thin slice CT scan capability has revolutionized lung resection strategies. With the advent of video assisted technology and keyhole surgical techniques, complications and post-operative morbidity from VATS is no higher than open thoracotomy (36-38). In ultra-high volume centers in China, the perioperative morbidity of thoracoscopic surgery is less than 0.1% (39,40).

MIS has made multiple resection possible with fewer adhesions allowing easier access to the pulmonary nodule for RPM with decreased morbidity and mortality rates (41-43). Thoracic centers have been adopting VATS as their main approach for RPM and non-anatomical resection the preferred technique (43). However, the issue with VATS procedure is the inability to bimanually palpate the whole lung to detect nodules which was missed during preoperative radiological examinations. Most pulmonary metastatic nodules are situated at the peripheral parts of the lung making easy detection and resection by VATS (44). The number of pulmonary nodules must be determined carefully by preoperative imaging and prognosticated as the survival outcome diminish if the numbers are 3 or more (12). A multidisciplinary treatment before subjecting a patient for repeat resections must be comprehensive and holistic in achieving a better outcome with adequate surgical margin and complete metastasectomy. In nodules which are small and multiple (3 and above), lesions can be missed in imaging and VATS. This shortfall can be overcome by changing strategy via hybrid VATS, whereby bimanual palpation can be done for detection and clearance.

In a case series done in Netherlands by Mutsaerts *et al.*, there was a significant higher number of complications (P=0.049) for thoracotomy compared to thoracoscopy procedure performed for lung metastatic lesions, though the 2-year disease-free interval and overall survival rate did not show significant difference (45). Meng *et al.* did a meta-analysis comparing 337 patients in VATS group versus 485 patients in thoracotomy group who underwent PM. The overall survival rate was significantly higher for VATS compared to thoracotomy, though there was no difference in recurrence free survival between the 2 groups (46). Kondo and colleagues studied the benefits of VATS for RPM and noted a shorter operating time, less intraoperative bleeding, and fewer complications compared to repeated thoracotomy. VATS was curative and not inferior to thoracotomy in terms of relapse rate post RPM (47).

Patients with bilateral pulmonary metastasis could also benefit from bilateral VATS or subxiphoid approach for gaining access to bilateral lung fields (48). Bilateral thoracotomy would be not suggested as post-operative recovery could be challenging with subsequent adjuvant treatment delays.

Lung parenchymal preservation and pain control are more effective in VATS compared to thoracotomy (49). Patients who underwent VATS for repeated surgical resection of metastatic lung nodules showed improved outcome for disease free survival and overall survival (15,23,50). Herle *et al.* demonstrated a better overall pulmonary recurrence with VATS compared to thoracotomy but the data compiled was not heterogenous concluding that VATS was another option for PM with equivalent survival and recurrence rate (51). Short-term outcome for VATS definitely has more benefits than thoracotomy and long-term outcome is rather the same.

Localization of metastatic nodules can be performed in preoperative or post-operative manner. Preoperative localization using CT guided dye injections using methylene blue or indocyanine green (ICG), and hook wire placement requires the aid of interventional radiologist. The disadvantages are, dye spread to non-target sites, pneumothorax, pain and rigid operative time arrangements. Preoperative bronchoscopy and targeted dye into the lesion or segment can be done. Again, missing the target and dye spread can occur. Further advancement will be the intra-operative localization techniques which is dynamic and more comfortable as the patient is anaesthetized. Bronchoscopy guided by electromagnetic navigation and dye injection into the target site with fiducial marker can enhance accuracy of localization achieving tumor clearance with margin.

Current advancement of robotic-assisted thoracic surgery (RATS), removal of nodules can be achieved in the same manner as in VATS or subxiphoid approach. Unfortunately, the cost benefit ratio of performing RATS is unjustifiable. However, RATS is useful if the tumour location is in complex central location requiring sleeve lobectomy. The spatial visualization as well as the wrist dexterity in robotic surgery will allow a safer and precise dissection with anastomosis.

Role of lymph node dissection in RPM

There is no proper consensus for lymph node removal during metastasectomy. Menna *et al.* found poorer survival benefit if nodes are positive (2). Forster *et al.* from Switzerland Lausanne University in their publication paper mentioned criteria for lymph node dissection during PM. It was only performed for lesions more than two centimeters diameter, centrally located, requiring anatomical resection, or when lymph node involvement was suspected by preoperative radiological examination (43). Hence lymph node removal does not confer any benefit from the survival stand point, but aids in onco-surgical decision-making capability for future metastasectomy and prognostication.

Strengths and limitations of this review

This review can be regarded as the first to study role of MIS for RPM. The references obtained for this review are from all parts of the world performing VATS and other modality of MIS for PM. Hence this review can be regarded as robust and applicable to clinical practice.

The limitation of this study is its low level of evidence. All the studies available are observational and retrospective studies. Furthermore, randomization without bias is nearly impossible to study the outcomes for MIS procedures especially with the advantages of MIS in short term perspective.

Conclusions

Extrapolating the available guidelines and evidence, it can be safely concluded that MIS for RPM is safe and effective method to achieve favorable long-term survival. The adaptation of hybrid VATS can be employed especially in nodules which are small and multiple to achieve complete clearance.

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