# Segmentectomy by video-assisted thoracic surgery for pulmonary metastases

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*Contributions:* (I) Conception and design: B Bédat; (II) Administrative support: B Bédat; (III) Provision of study materials or patients: B Bédat; (IV) Collection and assembly of data: B Bédat, F Triponez; (V) Data analysis and interpretation: B Bédat, W Karenovics, F Triponez; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** The lung is a frequent metastatic site of primary extrapulmonary cancers, such as breast cancer, colorectal cancer (CRC), melanoma, renal cancer and germ cell tumors. Pulmonary metastasectomy (PM) is widely performed in patients with limited lung metastasis, and contributes to approximatively 15% of all lung resections in Europe. According to national and international registries, non-anatomical wedge resection is the most common type of resection. Segmentectomy by video-assisted thoracic surgery (VATS) is not usual and is used mostly for central metastasis or in case of multiple metastases in the same segment. Few studies compared wedge resection and anatomical resection in the field of PM. Consequently, the extension of the lung parenchyma resection is debatable and there is no evidence to guide practice. However, recent studies showed a potential benefit of segmentectomy compared to wedge resection. Anatomical resection also seems to improve the nodal staging and would therefore allow for a better adaptation of systemic treatment. This narrative review provides an update on the surgical approach for metastasectomy. The technical aspect is discussed, as well as the extension of the parenchymal resection. We focus this narrative review on pulmonary segmentectomy for lung metastases, trying to justify its use by tumor biology and patient condition.

**Keywords:** Video-assisted thoracic surgery (VATS); segmentectomy; pulmonary metastasectomy (PM)

Received: 26 March 2020; Accepted: 14 July 2020; Published: 15 March 2021.
doi: 10.21037/vats-2020-lm-05
**View this article at:** http://dx.doi.org/10.21037/vats-2020-lm-05

## Introduction

The lung is a frequent metastatic site of primary extrapulmonary cancers, such as breast cancer, colorectal cancer (CRC), melanoma, sarcoma, head and neck cancer, renal cancer, germ cell tumors, and thyroid cancer (1,2). Surgery is widely used for patients with limited lung metastases, and contributes to approximatively 15% of all lung resections in Europe (3,4). The extension of the lung parenchyma resection is debatable and there is no evidence to guide practice. According to national and international registries, non-anatomical wedge resection is the most commonly performed type of procedure (5-7). Lobectomy or pneumonectomy seem to be preferred to pulmonary segmentectomy when larger resection is considered necessary (6-9). Pulmonary segmentecomy by video-assisted thoracic surgery (VATS) for lung metastasis is therefore relatively uncommon and poorly described.

This narrative review provides an update on the VATS segmentectomy approach for metastasectomy for primary extrapulmonary neoplasms, trying to justify this approach according to the tumor biology and patient characteristics.

## Tumor biology, phenotypes and extent of lung resection

Most cancers metastasize to specific organs, a process known as "organotropism". Organotropism is regulated by multiple factors, such as the circulation pattern, tumor-intrinsic factors (the “seed”), the host microenvironment (ME) (the “soil”), and the interactions between the migrating cells and the ME (1,10). In this “biological theory”, the complex ME of the lung appears to be particularly conducive to develop secondary lung neoplasms (2). The numerous capillaries provide opportunities for cancer cells to adhere. A pre-metastatic niche in the lung can be built by circulating factors secreted by primary cancer cells. For example, these factors can induce alveolar type II cells to secrete chemokines to recruit neutrophils (11). Another factor secreted by breast cancer cells can enhanced pro-inflammatory S100A4 expression in lung fibroblast to promote a pre-metastatic niche for lung metastasis (12). In addition, lung resident cells can create a pro-metastatic niche for many types of cancer by secreting chemokines, such as CXCL12 and CCL21 (13). Inflammatory cells in the lung can also help cancer cells evade immunosurveillance and promote their survival in the lung (14). Furthermore, pre-existing inflammation induced by cigarette smoking or obesity could contribute to increased lung metastasis in breast cancer (15,16). In contrast to the pro-metastatic niches, the lung also seems to have metastasis-suppressive niches, which inhibit cancer cell proliferation. For example, these metastastic-suppressive niches can induce metastatic dormancy in breast cancer (1). Inflammation could also be led to the awaking of these dormant tumor cells (17). At this stage, there are two hypotheses of metastatic progression: a linear model in which the primary tumor goes through several cycles of genetic transformation before highly malignant cells spread into the lung; and a parallel model in which metastatic spread is an early process that occurs when the primary cancer forms (18).

In contrast to this “biological theory”, the “mechanistic theory” established that small foci of tumors may be stopped at the end of the lung blood vessels because of their size. The lungs would therefore be the first “filters” for cancer cells, with the exception of digestive tract tumors for which the liver represents the first filter. It is possible that these two theories can co-exist. However, both theories can’t fully explain the notion of oligometastasis, which is a hypothetical translation state between localized and widespread systemic disease (19). Therefore, the concept of oligometastasis implies that a local control of oligometastasis could delay or avoid a systemic spreading. For this reason, pulmonary metastasectomy (PM) is currently referred to as a potential curative treatment in oligometastatic disease by some authors. However, there is no consensus on the definition of oligometastasis. The definition depends principally on the nature of the primary tumor, the time interval between the diagnosis of primary and diagnosis of oligometastasis, and the detection method sensitivity.

From the “mechanistic theory” emerged the hypothesis that a wedge resection, with resection of the tumor and distal vessels with free margins, is sufficient for a complete resection of metastasis. From the perspective of “biological theory” the concept of a local control of the metastatic disease is counter intuitive, particularly if a parallel model exists. Generally, the question arises of considering the visible metastatic disease as the “tip of the iceberg”. However, the phenotypic heterogeneity of the tumor means that cells originating from the same tumor may have different metastatic potential. The number of metastases from cells can vary even within the same clone (20). This heterogeneity could also partially explain the presence of oligometastasis. Nevertheless, according to Bayesian models, individuals may be rendered free of disease by treatment of limited metastases more frequently than standard predicted models (21). The author adds that the precise number of detectable metastases may be less important than the metastatic potential of the tumor, the anatomic distribution of the metastases, the disease-free interval, and chance. The decision to treat metastasis with curative intent is then justified in the context of providing “the benefit of the doubt” to the patient.

Therefore, the decision on the extent of pulmonary parenchymal resection seems difficult to take on the biological basis of the tumor. However, a recent study analyzed patients with lung metastasis of CRC with V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (22). They established that non-anatomical resections were associated with both worse overall survival (OS) and time to pulmonary recurrence as compared to anatomical resections (segmentectomy or lobectomy). They explained these results by the hypothetical presence of microscopic foci of cancer cells along the lung vasculature. Although there is not enough data in the literature to confirm this conclusion, another study showed that the KRAS mutation in CRC appears to be strongly implicated in an aggressive lung metastatic phenotype (23). Other gene signatures or microRNAs expression, could predict the pulmonary oligometastatic nature of the tumor (24,25). Furthermore, host genetics seem to be important in the oligometastasis setting (26). The impact of these signatures, the role of host and the type of lung resection on patient survival have to be better explored in clinical study.

 

## Anatomical metastasectomy

Despite an abundant literature, the level of evidence supporting the superiority of PM over a simple follow-up remains low, without a single randomized controlled trial (27). In highly selected population of patients with CRC, lung metastasectomy seems to be associated with a longer patient survival than those offered by conventional systemic treatments and most recent targeted therapies (28). PM appears to provide cure across multiple cancers when certain criteria are achieved, such as a control of the primary cancer, absence of extrathoracic metastasis, complete resection (R0), absence of lymph node involvement, disease-free interval, and the number of metastases (29-35). In a meta-analysis considering patients with lung metastasis of CRC, Gonzalez *et al.* showed some factors associated with prolonged survival after PM, such as prolonged disease-free interval, normal prethoracotomy carcinoembryonic antigen, absence of thoracic lymph node involvement, and a single pulmonary lesion (36).

Recently, the Society of Thoracic Surgeons (STS) decreed a consensus document to standardize the procedure (3). Considering the technical aspects of surgical PM, they recommended a minimally invasive surgery if free margins are accomplishable, a lymph node sampling/dissection, and to consider preferentially a less-than-lobectomy procedure allowing pulmonary parenchymal sparing, rather than a lobectomy or pneumonectomy. Indeed, previous studies showed that non-anatomical resection could improve long term survival if a free-margin can be obtained. Furthermore, resections can be safely repeated (37,38). Anatomical resections (segmentectomy or lobectomy) are then reserved for patients with large or central metastasis or in case of multiple metastases in the same lobe or segment. Consequently, few studies compared wedge resection and anatomical resection in the field of PM.

A recent study has compared wedge resection and segmentecomy in patients with CRC (39). It analyzed 553 patients, including 98 segmentectomies. The authors found that segmentectomy was associated with a better 5-year recurrence free survival (48.8% *vs.* 36%) and 5-year OS (80.1% *vs.* 68.5%). In the multivariate analysis, segmentectomy was a positive prognostic factor for recurrence (HR: 0.63; 95% CI, 0.44–0.87; P=0.005) but failed to be of significant difference in OS (HR: 0.65; 95% CI, 0.38–1.05, P=0.08). The authors explained this result by a better resection margin and lymph node evaluation in patients with segmentectomy. However, KRAS mutations were not evaluated in this study. Moreover, another study showed that spread through air space of floating clusters of cancer cells in pathological findings could be associated with local recurrence at the resection site despite a R0 resection (40). This could explain a decreased recurrence rate after segmentectomy, as compared to wedge resection. As the type of surgical procedure appears to affect rates of resection-margin recurrence, every possible effort for preventing resection-margin recurrence should be made. Another study analyzed 522 patients with lung metastasis from CRC comparing 104 patients treated with major anatomical resection (lobectomy and pneumonectomy) versus 418 patients with lesser resections including only 19 segmentectomies (41). In the multivariate analysis, they found that major resection appeared to be a protective factor for disease-specific survival (HR: 0.6; 95% CI, 0.41–0.96; P=0.031) and DFS (HR: 0.5; 95% CI, 0.36–0.75; P<0.001). They also found that major resections were associated with a higher number of lymph node removed, as compared to lesser resections (mean number of 6.8±5.6 and 4.6±5.1, respectively, P<0.001). The histological lymph node involvement was also significantly different between groups (13.6% and 2.9%, respectively, P<0.001). However, it is difficult to establish if the higher rate of lymph node involvement with major resections was associated with the larger size of the metastasis in this group, a different location of the metastasis or the better lymph node dissection. Furthermore, the study of Shiono *et al.* including 683 patients undergoing lobectomy for lung metastasis from various origins showed that the presence of mediastinal lymph-node metastasis was a significant predictor for poor outcomes (HR: 1.43; 95% CI, 1.07–1.90; P<0.002), but not the extent of the LN dissection (42).

## VATS segmentectomy, a good compromise?

The evidence on the benefit of anatomical resection for lung metastasis remains low. However, as described above, anatomical metastasectomy compared to wedge resection could improve the disease-free survival and the chance of cure for certain tumors and in certain patients. Anatomical resection also seems to improve the nodal staging and would therefore allow for a better adaptation of systemic treatment. However, these unproven benefits of anatomical resection must be balanced with the risks of such a procedure.

Concerning the surgical technique, open thoracotomy has been the gold standard for surgery of lung metastasis.

The main arguments were that (bi-manual) palpation allowed the discovery of unseen nodules at the pre-operative imaging, and that free margins were more easily obtained by an open technique. However, cross sectional imaging has now very high resolution and can detect very small nodule. The disease-free survival does not appear to be affected by the surgical approach for CRC (VATS versus thoracotomy) (43,44). According to the STS consensus, PM can be considered with a preference for minimally invasive surgery (MIS) owing to the shortened postoperative recovery and lessened effect on short-term quality of life (3). The choice of the minimally invasive approach remains a point of debate. In order to decrease the aggressiveness of the surgical care, Galvez *et al.* reported a non-intubated uniportal left-lower lobe upper segmentectomy (45). Although the comparative benefits and oncological outcome over standard intubated procedure in PM are not established, innovative and less aggressive surgery opens up new debates.

VATS segmentectomy has some advantages. Compared to lobectomy, VATS segmentectomy has been proposed as a parenchyma-sparing procedure and should result in better postoperative pulmonary function and a faster postoperative recovery than lobectomy (46). Furthermore, compared to wedge resection, the advantages of VATS segmentectomy is that a pre-operative localization by marker is not necessary, and also the possibility to remove multiple lesions in the same segment. We showed recently that VATS segmentectomy can be considered as a safe procedure with a mortality of 0.8% for all indications (47). In another study, the risk of complication after anatomical resection by VATS for metastasis seems to be lower than for lung cancer (OR: 0.32; 95% CI, 0.13–0.80: P=0.015) (48). Therefore, VATS segmentectomy for lung oligometastasis could be a good compromise in selected patients.

As an alternative to PM, stereotactic body radiotherapy (SBRT) is currently used in inoperable patients, and is usually associated with low morbidity and mortality. However, no randomized study compared SBRT and surgery for lung metastasis disease, and short and long results of SBRT are missing in large series. Furthermore, a recent study observed 21.8% and 41.8% of respiratory decline after SBRT at 2 and 4 years, respectively (49). Although SBRT should be proposed in inoperable patients, it suffers from several inconveniences: lack of diagnosis and tumor biology and a decline of respiratory functions. The comparison of respiratory functions after SBRT or PM has not yet been evaluated.

## Conclusions

The level of evidence supporting the superiority of PM over a simple follow-up remains low. VATS segmentectomy is currently used only for central metastasis or multiples metastases in the same segment. However, VATS segmentectomy with lymphadenectomy for extra-pulmonary metastasis could improve survival and decrease the rate of recurrence in selected patients and for certain tumors. This approach also helps preserve lung parenchyma. The role of the tumor genetics and phenotype, as well as the role of patient genetics on the tumor extension is a matter of concern. These factors could have an impact on the decision concerning the extension of the resection needed to cure or significantly prolong the life of the patient.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editors (Marcello Migliore and Michel Gonzalez) for the series "VATS in Lung Metastasectomy" published in *Video-Assisted Thoracic Surgery*. The article has undergone external peer review.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form, available at: http://dx.doi.org/10.21037/vats-2020-lm-05. The series "VATS in Lung Metastasectomy" was commissioned by the editorial office without any funding or sponsorship. FT reports personal fees from Medtronic, personal fees from Stryker/Novadaq, outside the submitted work. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/vats-2020-lm-05
**Cite this article as:** Bédat B, Demarchi M, Triponez F, Karenovics W. Segmentectomy by video-assisted thoracic surgery for pulmonary metastases. Video-assist Thorac Surg 2021;6:7.

 