



Pulmonary metastasectomy— is the extent of resection worth reconsidering?

Marcus Krüger^{1^}, Christian Biancosino^{2^}

¹Department of Thoracic Surgery, Hospital Martha-Maria Halle-Dörlau, Halle, Germany; ²Department of Thoracic Surgery, Helios University Hospital Wuppertal, University of Witten/Herdecke, Wuppertal, Germany

Correspondence to: Marcus Krüger. Department of Thoracic Surgery, Hospital Martha-Maria Halle-Dörlau, Röntgenstraße 1, 06120 Halle/Saale, Germany. Email: Marcus.Krueger@Martha-Maria.de.

Comment on: Prisciandaro E, Ceulemans LJ, Van Raemdonck DE, *et al.* Impact of the extent of lung resection on postoperative outcomes of pulmonary metastasectomy for colorectal cancer metastases: an exploratory systematic review. *J Thorac Dis* 2022;14:2677-88.

Submitted Aug 29, 2022. Accepted for publication Oct 09, 2022.

doi: 10.21037/jtd-22-1186

View this article at: <https://dx.doi.org/10.21037/jtd-22-1186>

Background

Pulmonary metastasectomy (PME) is one of the main therapeutic options with curative intent for selected patients with pulmonary metastases (PM) originating from various solid tumours, such as colorectal cancer (CRC) or renal cell carcinoma. PME is a widely performed operation and the theoretical concept of oligometastasis is also currently supported by gene expression analysis (1). Nevertheless, belief in its effectiveness is not universal as most data are primarily based upon registry data and surgical follow-up studies.

Depending on the size and clinical focus of the particular department, lung metastasectomy can account for up to 25% of thoracic surgery procedures (2). In carefully selected patients resections can be associated with prolonged relapse-free survival and cure (3). Resection even in repeat settings or in cases of simultaneous liver and lung affection has become a widely accepted treatment for appropriately selected patients.

Historically, Pastorino's publication of the International Registry of Lung Metastases in 1997 established the foundation for lung metastasectomy in clinical practice (4). This review observed 5,206 patients with different primary metastatic tumours with PM. The overall 5-, 10-, and 15-year survival rates were 36%, 26%, and 22%, respectively. Factors associated with a better prognosis were identified

and included disease-free interval of 36 months and a single metastatic lesion.

Basically, there is wide consensus on many aspects of PME as PM have to be completely resectable or the primary tumour is controlled or controllable. Other aspects remain contentious. In this regard, Prisciandaro's findings in their current article are timely and relevant and provide a representative overview of the most important literature (5).

Impact of the extent of lung resection

In their recent article entitled "Impact of the extent of lung resection on postoperative outcomes of pulmonary metastasectomy for colorectal cancer metastases: an exploratory systematic review" (5), the authors utilize the available literature to analyze a relevant topic of thoracic surgery: Does an extension of the resection in terms of an anatomical resection improve overall survival (OS) or recurrence-free survival (RFS)/disease-specific survival (DSS)? As explained by Prisciandaro *et al.* (5), "Therefore, the purpose of this systematic review is to assess the differences in short- and long-term outcomes depending on the surgical extent of PM with curative intent."

On the one hand, there are surgeons who favor lung parenchyma sparing procedures whenever possible, a complete resection provided. Other colleagues recommend anatomical resection to minimize the risk of

[^] ORCID: Marcus Krüger, 0000-0001-5250-5658; Christian Biancosino, 0000-0002-2530-4436.

local recurrences aiming at both potential improvement of survival and preventing complications due to local recurrences, which may be difficult to manage. Undoubtedly, this therapeutical regime requires a limited number of metastases and the size and location of the lesion have to permit such a decision taking.

The first important result of the current publication is the interestingly small number of available articles comparing anatomical and non-anatomical resections for PME: Thus, only three out of 432 papers were finally suitable for the systematic review.

A basic problem for comparison of extent of resection is the definition of major and lesser resection, which becomes obvious in the current publication, too.

These three publications compared the different modalities of resection:

- (I) Major resections (lobectomies and pneumonectomies) *vs.* lesser resections (wedge resections, anatomical segmentectomies and 5 atypical resections) (6).
- (II) Segmentectomies *vs.* wedge resections (7).
- (III) Lobar resection *vs.* sublobar resections (including anatomical segmentectomies) (8).

A limitation that should be taken into consideration is the different size of patients collectives in the two arms (the lesser resections were performed far more frequently) which leads to a diminished comparability with regard to the statistical analysis.

The review confirms the assumption that lesser resections are associated with a lower postoperative morbidity. Whereas mortality was comparable and fairly low [1% after lobectomy or pneumonectomy and 0.2% after lesser resections (6)] morbidity was higher following more extended resections (25% *vs.* 13.4%) in the study of Hernández *et al.* (6) and 14.3% *vs.* 5.3% in the study of Shiono *et al.* (7) respectively.

The study also revealed that non-anatomical resections are associated with a smaller rate of systematic lymphadenectomy or even lymph node sampling. In the study of Shiono *et al.* only in 25 out of 455 wedge resections (5.5%), lymph node assessment was performed. According to Prisciandaro *et al.*, a systematic lymph node assessment is an essential component of PMEs. But, there seem to be arguments for disregarding lymphadenectomy, especially in cases of video-assisted thoracoscopic surgery (VATS) wedge resections assuming that lymph node metastases are unlikely in case of inconspicuous preoperative diagnostic imaging. Additionally, lymph node sampling in case of limited small peripheral metastases is not likely to yield metastatic material but may

complicate a subsequent lymphadenectomy in case of future lymph node metastases.

A significantly higher incidence of resection-margin recurrences was observed in the study of Shiono *et al.* In a recent study the authors themselves investigated the influence of stapler line recurrences on OS. According to a preliminary analysis resection margin recurrences do not alter OS, provided systematic follow-up examinations and appropriate local therapy for corroborated local recurrences (Krüger, Biancosino, unpublished data). The interpretation of postoperative CT-scans regarding the differentiation between inflammatory changes and tumor recurrence, especially after laser resections, is a very important aspect and may be difficult so that these interpretations should be performed interdisciplinarily.

A significantly higher incidence of resection-margin recurrences was observed in patients who underwent non-anatomical resections. Laser resection shows a trend to minimize the risk of local recurrences whereas the impact of such procedures on OS remains uncertain.

In their current article Prisciandaro *et al.* come to the conclusion that “Anatomical resections of lung metastases from CRC seem to be associated with improved RFS.”

Several studies have investigated the benefits of repeated metastasectomy. We could however demonstrate in our own substantial collective that even repeat lung metastasectomy show a survival benefit provided that a close multidisciplinary evaluation has taken place (9). In this regard it has to be taken into consideration that possibly anatomical resections in the first place could limit the possibility of repeat metastasectomies.

Quo vadis PME—which trials can light us the right way?

The present article contributes to the effort of illuminating PME scientifically. This is in our opinion of paramount importance because due to the lack of prospective randomized data and their methodic limitations—as we still will see—it appears inevitable to create substantial data on PME even if they are not prospective and randomized.

Thitherto, there is still no randomized data proving a survival benefit from PME. Due to the lack of randomized data, clinical practice varies essentially between the different centers. The only published trial which was randomized in its study design and aimed at examining the benefits of PME was the PulMiCC (PME *vs.* Continued Active Monitoring in Colorectal Cancer) trial (NCT01106261) (10). It randomly

assigned 65 patients with metastatic CRC to PME or active monitoring. The study was stopped early for low recruitment. Thus, this trial remained underpowered to conclude that no surgery and surgery are comparable. PulMiCC has provided some additional evidence that a modest survival benefit may be associated with metastasectomy, but probably not as prominent as previous data suggests.

A further randomized phase II trial (NCT03599752) (11) investigates the multimodality treatment in risk-stratified CRC patients with lung metastases. The results of this study will help to understand the benefits which are associated with the combination of chemotherapy and PME.

There are at least three arguments supporting the hypothesis that prospective randomized data concerning lung metastasectomy alone will not be able to address all important aspects.

Moving target

The most convincing argument is the assumption that PME represents a moving target due to ongoing changes in therapeutic options for malignancies inducing lung metastases (12). This applies to both systemic and local therapeutic options, but it became particularly obvious with the introduction of targeted therapies and immunotherapies. This enhanced efficacy might even make PME no longer necessary in special cases. On the other hand, due to effective elimination of innumerable lesions, these agents may facilitate surgical resection of more manageable residual metastases, which might show a certain resistance towards the agents (13). Therefore, it appears inevitable to create as much data as possible other than prospective randomized trials.

Technical considerations

PME can be performed using a number of different surgical techniques, including conventional excision with electrocautery and laser-assisted surgery (LAS). However, the influence of surgical technique and approach on outcomes after PME are poorly studied. In particular, only a small number of studies have focused on outcomes after LAS. The same applies to the modality of resecting metastases by means of radial stapler (3).

Patient recruitment

Due to ethical aspects for a number of colleagues, it may be

questionable to enroll patients with one or two metastases into the control non-surgical group of the study. The PulMiCC Trial provided evidence supporting a randomized comparison of PME *vs.* no surgical resection from the ethical point of view. But to the best of our knowledge, the well-designed PulMiCC Trial was stopped due to poor patient recruitment so that the conclusion might not be sufficiently substantiated (10,14).

Summary

In summary, the article of Prisciandaro *et al.* (5) revealed an association between anatomical resections and an improved RFS. However, the available data, based on only 3 non-randomized studies, failed to show a positive effect on OS. There are several limitations of the study, such as the definition of the extent of the operation, substantial differences regarding the number of patients in the compared groups or substantial differences regarding lymphadenectomy. With regard to the rapidly evolving field of new systemic therapeutic agents the importance of lymphadenectomy is growing, since proved lymph node metastases may be an indication for a promising adjuvant systemic treatment.

According to Prisciandaro *et al.* (5), extent of resection should remain an individual decision depending on location of the tumor, tumor-size and other oncologic and patient specific features, such as disease-free survival (DFS), lung function, general performance and number of metastases.

Undoubtedly, selection of patients is a key factor in lung metastasectomy. Patient selection, however, should no longer only be seen as a problem for scientific evaluation, but more as a chance to cure these selected patients. Newly developed risk scores become increasingly meaningful and may facilitate decision making in the future. It should also not be neglected that PME can be beneficial concerning quality of life even if OS may not be enhanced when local morbidities and complication are to be feared like in cases of infiltration in other entities or infectious complications.

A close interdisciplinary co-operation is of paramount importance for the development of a therapy schedule and the implementation and surveillance of the oncologic treatment. A further main result of the recent article by Prisciandaro *et al.* is the higher incidence of local recurrences following wedge resections. This underlines the importance of a systematic oncologic follow-up aiming at early detection and consequent local therapy of recurrent metastases, especially in the case of stapler line recurrences.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1186/coif>). The authors have no 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Lussier YA, Khodarev NN, Regan K, et al. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. *PLoS One* 2012;7:e50141.
- Internullo E, Cassivi SD, Van Raemdonck D, et al. Pulmonary metastasectomy: a survey of current practice amongst members of the European Society of Thoracic Surgeons. *J Thorac Oncol* 2008;3:1257-66.
- Mangiameli G, Cioffi U, Alloisio M, et al. Lung Metastases: Current Surgical Indications and New Perspectives. *Front Surg* 2022;9:884915.
- Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37-49.
- Prisciandaro E, Ceulemans LJ, Van Raemdonck DE, et al. Impact of the extent of lung resection on postoperative outcomes of pulmonary metastasectomy for colorectal cancer metastases: an exploratory systematic review. *J Thorac Dis* 2022;14:2677-88.
- Hernández J, Molins L, Fibla JJ, et al. Role of major resection in pulmonary metastasectomy for colorectal cancer in the Spanish prospective multicenter study (GECMP-CCR). *Ann Oncol* 2016;27:850-5.
- Shiono S, Okumura T, Boku N, et al. Outcomes of segmentectomy and wedge resection for pulmonary metastases from colorectal cancer. *Eur J Cardiothorac Surg* 2017;51:504-10.
- Li H, Hu H, Li B, et al. What is the appropriate surgical strategy for pulmonary metastasis of colorectal cancer? *Medicine (Baltimore)* 2020;99:e21368.
- Krüger M, Franzke K, Rajab TK, et al. Outcome of Repeat Pulmonary Metastasectomy. *Adv Exp Med Biol* 2021;1335:37-44.
- Treasure T, Farewell V, Macbeth F, et al. Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. *Trials* 2019;20:718.
- clinicaltrials.gov. Chemotherapy and/or Metastasectomy in Treating Patients With Metastatic Colorectal Adenocarcinoma With Lung Metastases. Available online: <https://clinicaltrials.gov/ct2/show/NCT03599752>
- Rusch VW. Pulmonary metastasectomy: a moving target. *J Thorac Oncol* 2010;5:S130-1.
- Cheung FP, Alam NZ, Wright GM. The Past, Present and Future of Pulmonary Metastasectomy: A Review Article. *Ann Thorac Cardiovasc Surg* 2019;25:129-41.
- Sponholz S, Oguzhan S, Mese M, et al. The impact of primary tumor location on prognosis after colorectal lung metastasectomy. *Int J Colorectal Dis* 2021;36:1731-7.

Cite this article as: Krüger M, Biancosino C. Pulmonary metastasectomy—is the extent of resection worth reconsidering? *J Thorac Dis* 2022;14(11):4202-4205. doi: 10.21037/jtd-22-1186