Editorial

Anatomical resection of colorectal lung metastases: a reasonable indication without evidence—non-systematic and incomplete reporting is a key issue

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The treatment of pulmonary metastases is a subject of debate in terms of indication, technical execution and interpretation of results. Insofar as lung cancer arises from a single site and from a single malignant cell with exponential growth and subsequently the local spread through the lymphatic system, radical local treatment is rational and proved by randomized trials. The situation is very different in the treatment of pulmonary metastases. Detached from the primary tumor site circulating tumor cells (CTC) are filtered in the lung capillaries and build solid tumor nodules. At the time of pulmonary metastasectomy, the patient has objective tumor nodules and occult metastases in the lung that cannot be detected intraoperatively. Therefore, the standard of care is to resect the local metastasis with an adequate safety margin to prevent local intrapulmonary recurrence, but to preserve as much functional tissue as possible (1). Many prognostic factors with various influences on survival have been described which determine the success of pulmonary metastasectomy, such as synchronous *vs.* metachronous patterns, disease-free interval (DFI), number of metastases, size of metastasis, lymph node involvement, completeness of resection, operative technique used for resection, response to preoperative chemotherapy, systemic therapy in the course of the disease, and others (2,3). They all make it very difficult to attribute a permanent success of surgical therapy to a single aspect. The amount of tissue resected may also, under certain circumstances, affect long term outcome.

In particular, the question of whether anatomical resection is more favorable than wedge resection in metastasis surgery, will be biased by many other prognosticators. Anatomical instead of wedge resection may yield 3 advantages for the patient:

(I) The larger amount of tissue removed reduces the number of occult metastases in healthy lung tissue and should thus reduce the occurrence of intrapulmonary new metastases.
(II) Removal of intralobar or intrasegmental lymphoid tissue may include undetected lymph node metastases or lymph vessels involvement and thus may reduce locoregional recurrence.
(III) Finally, anatomical resection attributes to greater safety margins and reduces the risk of local intrapulmonary recurrence at the resection margin.
(IV) But the technical applicability of anatomical resections is limited by the number of metastases in different lobes.

These hypothetical advantages of anatomical resection over wedge resection should translate into a reduction of local and locoregional recurrences, increased disease-free survival (DFS), recurrence-free survival (RFS), cancer specific survival (CSS) and the percentage of pulmonary recurrence-free patients. However, these effects can only be expected, when they are not jeopardized by other confounding factors, such as additional wedge resections, multiple lesions, lymph node involvement, other organ manifestation or other important prognosticators. And improved overall survival (OS) can only be imagined in

those patients in whom local tumor recurrence has been prevented by anatomical resection and no new metastases in other locations have risen.

Prisciandaro *et al.* (4) used a systematic review to answer the question of whether anatomical resection rather than wedge resection can be beneficial for enhancing local intrapulmonary control in metastasis surgery. Special attention was paid to the impact of the extent of resection on short- and long-term outcomes. Using the PRISMA reporting checklist, the authors identified 432 papers through a literature search and ultimately included 3 retrospective studies in a final systematic review of 1,342 patients (5-7). At that time, a major problem became apparent: despite the vast amount of literature on metastasis surgery, the issue of anatomical versus non-anatomical resection was rarely addressed and survival and outcomes were not analyzed with respect to the amount of tissue removed. This systematic review found that all selected studies reported significantly longer RFS after anatomical resections, whereas OS was not different from non-anatomical resection. Therefore, the authors concluded that „the reported findings prevent us from recommending anatomical lung resections for CRC metastasis". However, the authors point out that other studies not included in this review report increased RFS and OS after anatomical metastasis resection, for example in colorectal cancer (CRC) metastases with KRAS-mutation (8).

Analyzing three papers (5-7), Prisciandaro *et al.* (4) made several relevant observations:

(I) The extent of lung resection was influenced by the size of the metastases. They were significantly ($P<0.001$) larger in the anatomical resection or major resection groups.

(II) None of the included studies took the location of the lesion within the parenchyma into account.

(III) The incidence of resection margin recurrence was higher in the non-anatomical resection group, but none of the studies reported the size of safety margins.

(IV) Hilar and mediastinal lymph node dissection was more frequently performed in anatomical resections.

These differences raise the question whether it is the size of the metastasis or its central location that leads to anatomical resection, and wedge resection would not be an alternative. In this case, the comparison of wedge resection with anatomical resection would be obsolete. Secondly, increased RFS may be a result of radical lymphadenectomy or at least more reliable lymph node sampling during anatomical resections. And thirdly, adequate safety margins after wedge resection are a prerequisite for good quality surgery (9). It is essential to have knowledge of this, but it has not been reported. This might hide the fact that local recurrence after wedge resection was a consequence of inadequate surgery and inadequate safety margins. These remaining questions in all three papers are further complicated by significant differences between these studies, which are summarized in *Table 1*.

This table uncovers one important thing: there is a lack of systematic reporting, a lack of standardized operative treatment, a lack of systematic follow up in our thoracic surgery community and a paucity of inclusion criteria in these retrospective analyses. The inclusion of multiple metastases makes it difficult to assign tumor recurrence to a resection method, the non-systematic use of preoperative chemotherapy, non-systematic lymph node removal, and the inclusion of patients with extrathoracic lesions leads to confusion. Prisciandaro *et al.* (4) summarized these dilemmas as the main limitations of their systematic review: wide "heterogeneity in describing baseline characteristics and outcome measures" concerning the included studies. As a consequence, they suggest propensity score matching to stratify patients according to the number and size of metastases, clinical hilar-mediastinal nodal status, DFI and respiratory function to allow unbiased comparisons of anatomical *vs.* non-anatomical resections.

To our understanding, propensity score matching is not enough to overcome all bias:

(I) Outcome comparison of wedge resection with anatomical resection only makes sense if wedge resection would technically be an alternative. Therefore, central tumor location should be excluded and the technical feasibility of wedge resection should be confirmed for each case.

(II) Including cases with multiple metastases carries the risk that tumor recurrence or even local recurrence cannot be attributed to the index site. In general, the risk of tumor recurrence grows exponentially with the number of metastases removed. Furthermore, a patient after 5 wedge resections cannot be matched to the one after several lobectomies…

(III) As discussed in the current paper, OS is a function of many prognostic factors like the number of metastases, DFI, lymph node involvement, elevated carcinoembryonic antigen (CEA) and others (6,10,11), and is therefore not the adequate outcome measure to prove the benefit of anatomical instead

Table 1 Differences of the three analyzed papers on anatomical *vs.* non-anatomical resection of CRC lung metastases

Parameter	Hernández 2016	Shiono 2017	Li 2020
Number of patients	552	553	267
Male, n (%)	335 (64.2)	314 (56.8)	159 (59.6)
Age, years	64.5	66	59
Median follow-up (months)	38.7 (range, 0.7–60.3)	64.8 (95% CI: 62.4-67.2)	32.5 (range, 7.2–104.7)
Tumor biology			
Median DFI (months)	N/A	18	N/A
Synchronous, n (%)	N/A	146 (26.4)	N/A
DFI <12 months, n (%)	214 (34.9)	N/A	94 (35.2)
DFI ≥12 months, n (%)	338 (65.1)	N/A	173 (64.8)
Number of PM, n (%)	1 to >3	1 (range, 1–8)	1 (100.0)
1	248 (44.9)	N/A	267 (100.0)
>1	304 (55.1)	N/A	0 (0.0)
Tumor stage, n (%)			
LN examined	145 (27.8)	N/A	106 (39.7)
LN involvement	26 (5.0)	N/A	13/106 (12.3)
N0	119 (22.9)	N/A	N/A
Previous liver metastases	147 (28.2)	139 extrathoracic (25.1)	N/A
Colon	252 (48.6)	251 (45.4)	N/A
Rectum	234 (45.1)	297 (53.7)	N/A
CEA >5	190 (34.4)	178 (32.2)	N/A
Surgical characteristics			
Chemo before resection of PM, n (%)	111 (21.3)	0	N/A
Adjuvant chemotherapy after metastasectomy, n (%)	316 (60.5)	265 (47.9)	267 (100.0)
Extent of lung tissue removed	Lobectomy + pneumonectomy *vs.* sublobar	Segmentectomy *vs.* wedge	Lobectomy *vs.* sublobar (wedge + segmentectomy)
Recurrence analyzed	Local (scar); pulmonary (lung + LN); non-pulmonary	Resection margin, lung parenchyma new, LN mediastinum/ hilus, Extrathoracic	Tumor recurrence, no further differentiation

CRC, colorectal cancer; DFI, disease free interval; PM, pulmonary metastases; LN, lymph node; CEA, carcinoembryonic antigen; N/A, not analyzed.

of wedge resection. Only the rate of intrapulmonary local and locoregional recurrence can be used to compare different resection approaches.

(IV) Reporting of safety margin around the metastasis, especially after wedge resection, is necessary as local recurrence is a consequence of inadequate resection margins, and aggressive local tumor spread (9,12,13).

Regarding the technical performance of anatomical and non-anatomical resections, Nelson *et al.* estimated that achieving safety margins of at least half the tumor size led to local recurrence risk of less than 11% within 2 years. Furthermore, the relationship of tumor size and length of safety margins were inversely correlated: safety margins of 2 cm for 1cm tumors had a recurrence risk of 4.97%. On

the other hand, 2 cm tumors resected with 1 cm margin had a recurrence rate of 11.09% (9). This indicates that larger margins led to a reduced risk of local recurrence. Thus, it may be concluded that the increased rate of local recurrence after wedge resection is not a problem of the method, but of small safety margins. Reporting safety margins is necessary for future studies.

Furthermore, the reporting of local recurrence in the literature covers a wide range of possibilities: tumor recurrence in the same lung, same lobe, same segment or even a precise description like: increasing size of a lung nodule in a minimum of two separate CT evaluations, the presence of scar formation between the nodule and visceral pleura as residual from a prior surgery, nodules located in the same segment of a former metastasectomy, metal remnants in the lesion after wedge resection with staplers or intrapulmonary marking with clips. Histologic criteria after repeat metastasectomy should be: tumor around the staple line, identical tumor attached to, or within a scar formation (14). Li *et al.* (7) did not report the location of tumor recurrence at all. Shiono *et al.* (6) reported "resection-margin recurrence after pulmonary metastasectomy" and only Hernández *et al.* (5) differentiated "local recurrence (recurrence in the surgical scar), pulmonary recurrence (lymphatic/lymph nodes or lung tissue different from the surgical scar of previous pulmonary metastasectomy)". This precluded the evaluation and comparison of the most important outcome parameter: rate of intrapulmonary local recurrence.

Thus, in evaluating the huge work of Prisciandaro *et al.* (4) we congratulate them and think they got the best out of the currently insufficient literature and found significantly increased RFS after anatomical resection of CRC lung metastases. Giving the extensive discussion section, the authors listed many limitations and concluded that anatomical resection cannot be recommended for CRC lung metastases, referring to the included studies.

As a task for the future, a possible benefit of anatomical resection over wedge resection can only be evaluated by the use of multi-institutional prospective databases and exclusion of as many confounders as possible, then performing a propensity score matching to eliminate the remaining ones.

Future studies should include:

(I) Single metastases only, as they have the highest probability of cure after pulmonary metastasectomy (15).
(II) Anatomical (lobectomy) resection only in a case were wedge resection would have been an alternative (exclusion of central lesions).
(III) At least systematic lymph node sampling in all cases to allow stratification of lymph node status.
(IV) Systematic reporting of comorbidity and pulmonary function allowing lobectomy when necessary.
(V) Reporting of the completeness of resection and minimal safety margin.
(VI) Complete and systematic reporting of all prognosticators like primary tumor stage, DFI, extrathoracic metastases, metastasis size, lymph node involvement, CEA.

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