VATS anatomical resection (lobectomy or segmentectomy) for pulmonary metastasis

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Abstract: Metastasectomy is steadily gaining place in the arsenal of treatments of patients suffering from lung metastasis of colorectal carcinoma (CRC). Meanwhile thoracotomy has been the gold standard approach during years for lung metastasectomy of CRC, the use of video-assisted thoracic surgery (VATS) in this field is currently thriving. Indeed, in addition of known advantages of minimally-invasive surgery, VATS has shown equivalent oncologic outcomes in comparison to open techniques. Otherwise, several questions in the management of these particular patients remained unsolved. In particular, only few studies have explored the role of anatomical resections (i.e., segmentectomy/lobectomy/pneumonectomy) compared to wedge resections. Despite their low level of evidence, these studies highlight interesting preliminary results, in particular a survival advantage of anatomical resections over non-anatomical. Most recent works have even suggested a potential role of molecular markers to select candidates who would benefit from an anatomical resection.

Keywords: Lung metastasectomy; pulmonary metastasis; segmentectomy; lobectomy; video-assisted thoracic surgery (VATS)

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Lungs are very common sites of metastasis for a large variety of solid tumors (1). This may be partially explained by the fact that both lungs receive the blood from the whole body, and may serve as a filter for cancer cells, allowing them to proliferate in lung parenchyma. In daily practice, metastasis from colorectal cancer (CRC) is the most frequent situation encountered by thoracic surgeons, explaining the high number of publications on this topic. Even though there is so far no high level of evidence supporting the superiority of lung metastasectomy of CRC over a simple follow-up (2), the very large majority of surgical teams have included lung metastasectomy in the arsenal of treatment that can be offered to patients in a curative intent. Indeed, in highly selected population of patients, data published on survivals following lung metastasectomy are longer than those offered by conventional systemic treatments and most recent targeted therapies (3).

Because surgery can be morbid and always alters the respiratory function, several risk factors of poor outcomes after surgery have been identified by meta-analysis (4). These factors may help the clinicians to properly define patients who would benefit from surgery in case of lung metastasis. Hence, more than 1 lung metastasis, a short disease-free interval, a thoracic lymph node involvement, history of extra-thoracic metastasis and a high pre-operative level of carcinoembryonic antigen (CEA) have been identified in CRC as risk factors of worse survival after surgery. Since they are reflections of an aggressive disease,

Figure 1 VATS left upper lobe segmentectomy for metastasis (10). Available online: http://www.asvide.com/watch/32936

even though they were highlighted following studies on CRC, it seems reasonable to think that they could be applied to other solid tumors (excluding pre-operative CEA). Otherwise, more recently, the increase in molecular techniques have led to a better understanding of molecular alterations of cancer, allowing clinicians to better define prognosis of patients and offer more adapted treatment. Here again, in the field of lung metastasis, CRC have been the most studied. Hence, one molecular alteration has been extensively studied: the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog mutation (*KRAS*) (5,6). Even though their places are not well defined in the decision making before surgery and deserve further studies, *KRAS* and other molecular alterations seem to be very interesting and promising biomarkers, defining different subgroups of patients.

For decades, open thoracotomy has been the gold standard for surgery of lung metastasis, based on 2 major arguments to support this approach: (I) the whole lung can be palpate by surgeons during a thoracotomy, looking for unseen nodules at the pre-operative imaging, (II) free margins were more easily obtained by an open technique. However, it has been shown by previous authors that more than 40% of nodules measuring less than 5 mm are benign (7), questioning whether palpation of the lung may lead to an over-resection of healthy parenchyma. More, it seems that there is no survival difference between video-assisted thoracic surgery (VATS) and thoracotomy, leading to hypothesize that those small "missed" nodules might not impact survival (8). Finally, current recommendations of free margins, between 0.5 and 1 cm, are easily attainable by VATS. On the other hand, VATS resection has shown a lot of benefits compared to open thoracotomy, in particular: less pleural adhesions making re-surgery easier, less post-operative pain, faster recovery and better compliance to adjuvant chemotherapy (9). All of these making VATS an acceptable approach for lung metastasectomy of CRC (*Figure 1*).

Owing to the risk of lung recurrence, it is usually recommended to perform lung parenchyma-sparing surgery, particularly non-anatomical resections (i.e., wedge resections). Indeed, previous publications have shown that non-anatomical resections can lead to long term survival, and repeated resections can be safely performed and are associated with long survival if a R0 resection can be obtained (11,12). However, repeated thoracic procedures increase the post-operative morbidity, and disease recurrence and progression can always lead to the death of the patient. So far, there are no robust evidence in the published literature supporting the realization of wedge resection in case of lung metastasectomy. This attitude is based on the speculation that once in the general circulation, small foci of tumors may be stopped at the very end of the lung blood vessels because of their size, allowing cancer cells to proliferate there. This has been used by authors to explain the higher observed frequency in daily practice of rectal cancer metastasis to the lung, compared to colon cancer. Indeed, the venous drainage of the upper two-thirds of the rectum is directly performed by the inferior vena cava, making lung the first "filter" for cancer cells, meanwhile the venous drainage of the colon and the lower third of the rectum is performed by the portal system, making the liver in this case the first "filter" (13). Nevertheless, in this "mechanistic theory", because tumor cells are stopped at the very end of the vessels, it has been hypothesized that wedge resections, removing the tumor, the surrounding parenchyma with free margins, and the end of the vessel might be sufficient to obtain a R0 resection. However, this technique has led to a non-insignificant number of recurrences, leading authors to question the place of anatomical resections in this indication.

The study from Ginsberg and colleagues, published in 1995, showing a higher rate of locoregional recurrence and death after wedge resection, has led to the adoption of anatomical resection in the field of primary lung cancer by the community of thoracic surgeons (14). Despite no anatomical and/or *in vivo* studies, it has been hypothesized that wedge resections may lead to leave in place cancer cells in the zone of drainage of the pulmonary segment/lobe. Because anatomical resections, such as segmentectomy and lobectomy, are usually reserved in case of large and/or centrally located lesions not accessible to a wedge, or

multiple lesions in the same segment/lobe, few studies are available in the field of lung metastasectomy, and again, are mainly available from lung metastasis of CRC. Recently, Shiono *et al.*, considering 553 patients (98 undergoing segmentectomy), found a better 5-year recurrence free survival (48.8% *vs.* 36%) and 5-year OS (80.1% *vs.* 68.5%) in cases of segmentectomy (15). They concluded that segmentectomy was a positive prognostic factor for recurrence using multivariate analysis (HR: 0.63; 95% CI, 0.44–0.87; P=0.005) but failed to find a significant difference in OS, although the difference did approach significance (HR: 0.65; 95% CI, 0.38–1.05, P=0.08). In line with these results, Hernandez *et al.* published a prospective multicenter study (GECMP-CCR) on 522 patients, and although the study focused on lobectomies and pneumonectomies, it also demonstrated better disease-specific survival and DFS in cases of major ARs compared to lesser resections, particularly wedge resections (16). These better results for AR could be indirectly related to the lymphadenectomy performed, particularly in stations 11 to 14, leading to a more accurate lymph node staging, and adaptation of adjuvant treatment. Indeed, lymph node involvement associated to lung metastasis has been shown to reach up to 50% (17). Based on a previous work published on liver metastasis, our group hypothesized that chemotactism to the lungs of CRC cells harboring *KRAS* mutations may lead to different modes of dissemination compared with wild type (WT) CRC cells, in particular with the persistence of small foci of cancer cells in vascular structures (18). We hence demonstrated in a multi-institutional international study that in *KRAS* mutated patients non anatomical resections were associated, in multivariate analysis, with both worse overall survival (HR: 6.524, 2.312–18.505, P<0.0001) and time to pulmonary recurrence (HR: 5.273, 1.731–16.064, P=0.003), meanwhile type of resection did not significantly affect outcomes of WT patients. More, we observed that resection-margin recurrence rate was not impacted by the type of procedure in WT patients (17.6% in case of segmentectomy *vs.* 19% in case of wedge (P=0.97), while it was significantly higher in case of wedge resection in *KRAS* mutated patients (54.2% *vs.* 4.8%, P=0.001) (19). Our observations support that the "mechanistic" theory of metastatic spread might at least partially explain lung metastasis of CRC, particularly in WT patients. More recently, the increased knowledge of the molecular alterations of cancer cells brought Stephen Paget "seed and soil" theory up to date, in which the cancer cell (the seed) needs an appropriate environment (the soil) to proliferate. Hence, although the molecular mechanisms are not yet fully understood, it is now largely believed that CRC harboring *KRAS* mutations have high tropism for the lung (20). Nevertheless, there are not enough data in the literature to reach firm conclusions on the presence of microscopic foci of cancer cells in the lung vasculature to explain the benefit of AR in *KRAS* patients. However, Urosevic *et al.*, using CRC cell lines harboring the *KRAS* G12V mutation, concluded that the downregulation of p38 MAPK signaling results in the increased expression of the cytokine parathyroid hormone-like hormone, which contributes to CRC cell extravasation to the lung by inducing caspase-independent death in endothelial cells of the lung vasculature, thereby increasing lung endothelial permeability (21). However, these data were reported for *KRAS* G12V mutations, but it is known that activated downstream signaling differs according to the amino-acid substitution. Hence, both *KRAS* G12C and G12V mutations exhibited activated Ral signaling and decreased growth factor-dependent Akt activation, whereas the G12D mutation exhibited activated PI3K and MEK signaling (22). One can therefore speculate that the mode of dissemination to the lung may vary depending on the amino-acid substitution and that the benefit of AR may also vary. Unfortunately, because of the small sample size of our cohort, we were not able to perform statistical analyses according to amino acid substitution. However, the central role of neutrophils in the metastatic process is emerging (23). In particular, it has been reported that neutrophils can induce cancer cell extravasation via the secretion of interleukin-1b and matrix metalloproteinases (24). Recent data have also highlighted the relationship between cancer cells harboring *KRAS* mutations and neutrophils. Indeed, in multiple mouse models of KRAS-driven lung cancer, it has been shown that *KRAS* signaling is responsible for the direct upregulation of neutrophil-related cytokines such as GM-CSF and CXCL8, thereby increasing the number of neutrophils in circulation and favoring NETosis (25). Furthermore, in chemical-induced colon and skin cancer models, the depletion of neutrophils or inhibition of CXCR2 signaling reduced the number of lung tumors in *KRAS* mutant tumors models, showing the partial dependence of KRAS tumors on neutrophils to develop metastasis (26). Considering these observations, one can hypothesize that foci of cancer cells may persist along the anatomic vascular structures of the lung in *KRAS* mutant CRC, thus explaining the benefit of AR in *KRAS* patients.

In conclusion, meanwhile VATS has largely shown its feasibility and safety, there are so far no enough data in

the literature to clearly evaluate the place of anatomical resections in the management of lung metastasis of solid tumors, which were for the very large majority of data obtained on CRC cells. However, the preliminary data are very interesting and are in favor of different mode of disseminations of cancers cells according to mutational status, leading to the necessity of practicing different type of resections. Hence, it seems that anatomical resections should not be only limited to centrally located and/or multiple lesions in the same anatomical region. Molecular markers might help surgeons in the future in the decision-making before surgery, not only to select good candidates for surgery, but also to decide which kind of procedure should be performed. However, due to the very large molecular heterogeneity between different solid tumors and among CRC cells, further studies are necessary to conclude and elaborate recommendations.

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