



# More is more in pulmonary metastasectomy?

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Approximatively 20% of patients with colorectal cancer (CRC) will develop distant metastases with liver and lung being the most frequent sites (35% and 10%, respectively) (1). The management is generally palliative due to the frequent invasion of other organs. However, in selected patients, pulmonary metastases (PM) from CRC may be surgically managed with curative intent based on well-defined criteria: no distant metastases; lung metastases are resectable; patient can tolerate the surgery. This local aggressive approach is credited with a 5-year survival rate of >50%, thus could provide survival benefits for selected patients with lung metastases. Classically, the main goal of pulmonary metastasectomy is to achieve a complete resection of the metastases while preserving as much pulmonary parenchyma as possible. Thus, for peripheral lesions, resection is generally accomplished by wedge technique. This procedure can be repeated in the event of local recurrence. It is nowadays routinely performed by video-assisted thoracic surgery (VATS) to accelerate recovery and decrease post-operative complications, since this approach is associated with virtually no morbidity. This aspect is particularly relevant in metastatic patients, for whom quality of life is crucial. On the other hand, for central lesions, an anatomical resection (segmentectomy, lobectomy or pneumonectomy) may be necessary to ensure a complete resection. The recent European Society of Thoracic Surgeons (ESTS) database analysis reported that surgical resections were managed by wedge or local excision in 61% of cases and anatomical resection in 39% (lobectomy: 26%; segmentectomy: 11%; bilobectomy:

1%; pneumonectomy: 1%) (2). These recent results are quite similar to those reported in the international registry and published in 1997 (33% of anatomical resections). Generally, the extent of the resections for colorectal cancer metastases is mainly based on the number of lung metastases and their location. Yet, few reports have analysed the impact of the surgical extent on patient survival. In the Spanish prospective multicenter study, Hernández reported that anatomical resection was necessary in 19.9% of 522 patients (3). Interestingly, anatomical resection appeared to be associated with a decreased HR for DSS [hazard ratio (HR) 0.6, 95% confidence interval (CI): 0.41–0.96,  $P=0.031$ ] and DFS (HR 0.5, 95% CI: 0.36–0.75,  $P<0.001$ ).

In the context of colorectal cancer pulmonary metastases, several elements may explain these results: the extent of the resection, the presence of spread through airways (STAS) and the importance of lymph node involvement.

In colorectal cancer patients, a major site of recurrence after wedge resection is the surgical margin, reported in 3.9% to 27.9% of cases (4,5). Welter *et al.* have demonstrated that in these patients, local recurrence rate after pulmonary metastasectomy was increased when the PM size was >5 mm and the safety margin <7 mm (6). In that sense, anatomical resection (by either segmentectomy or lobectomy) may potentially assure a better surgical margin than a wedge resection if deeply located metastases cannot be located during surgery or when the tumor is large. An attempt should be made to obtain a margin equal to or greater in length than the tumour size to minimize the risk of local recurrence (7).

Furthermore, STAS has been associated with an increased risk of local recurrence and is recognized as a poor prognostic factor (8,9). STAS, which is defined as the spread of cancer cells into air spaces in the lung parenchyma beyond the edge of the tumor, has been reported in up to 42% of PMs resulting from CRC. Considering the possibility of STAS in a significant number of cases, an extension of the surgical margin by anatomical resection should be proposed in case of large metastases.

The invasion of hilar or mediastinal lymph node involvement has been reported as an important prognostic factor of worse outcome (10). However, the impact of lymph node sampling/dissection in the context of pulmonary metastasectomy remains controversial. In a systematic review of the literature comprising 3,619 patients with colorectal pulmonary metastases, the five-year overall survival rate for all patients with lymph node metastases was 18.2% compared to 51.3% for patients without lymph node metastases (11). However, lymph node sampling or dissection is not a common surgical procedure in the management of PMs. Indeed, in international registry of lung metastases based on 5,206 patients reported in 1997 (12), lymph node sampling was performed in only 4.6% of patients. However, lymph node assessment was carried out in 58% of cases when a lobectomy was performed (2).

In this context, the systematic review proposed by Prisciandaro and colleagues is relevant. They performed a systematic review to assess the difference in short- and long-term outcomes depending on the surgical extent of pulmonary metastasectomy (13). Three retrospective studies were selected, including 1,342 patients. Unfortunately, a meta-analysis could not be carried out due to the major heterogeneity of the studies. For example, one study compared major resections (pneumonectomy and lobectomy) with lesser resections (wedge and segmentectomy), another study compared segmentectomy with wedge resection and the last one compared lobectomy with sub-lobar resection (segmentectomy and wedge). Not surprisingly, the extent of lung resection was influenced by the size of the metastases. However, none of these studies considered the location of the metastases (central *vs.* peripheral) to explain the extent of resection. In two studies, anatomical resections were protective factors for recurrence-free survival (RFS), and margin recurrences were more frequently observed in the wedge resection groups. However, the overall survival did not differ between patients who underwent anatomical resection or wedge resection. The lymph node assessment was also more

frequently performed in the anatomical resection groups.

Overall, the level of evidence of the selected studies remains low. Each of the three studies suffers from significant biases. The heterogeneity of the three studies does not allow a meta-analysis and the conclusion of this review should be considered cautiously. Certain studies may imply that lobectomies could be associated with better results, but we do not think that it can be a systematic conclusion. However, lobectomies could be performed in the event of central, large, or multiple metastases in the same lobe with acceptable results. It is important to perform the most conservative surgery in metastatic patients (14). A wedge resection by VATS seems to be the best procedure with low postoperative morbidity (5.2% of patients) (15). Furthermore, given the high risk of recurrence of this procedure (30%), it is important to perform a lung-sparing procedure (16).

This does not weaken in any way the methodological strength and reproducibility of the systematic review proposed by Prisciandaro and colleagues. This systematic review shows us the knowledge gap about pulmonary metastasectomy and the need to homogenize the variables of future studies.

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