



Video-assisted thoracoscopic surgery in lung metastasectomy— what is new in lung metastasectomy: an over-view

Jorge Hernández^{1^}, Juan J. Fibla¹, Laureano Molins^{1,2}

¹Service of Thoracic Surgery, Hospital Universitari del Sagrat Cor, Barcelona, Spain; ²Service of Thoracic Surgery, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Correspondence to: Jorge Hernández, MD, Service of Thoracic Surgery, Hospital Universitari del Sagrat Cor, C/ Viladomat 288, E-08029 Barcelona, Spain. Email: jhes.82@gmail.com.

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After the publication of the results of the International Registry of Lung Metastases (1), there was a great impact on the clinical practice of metastatic lung disease and its surgical management. According to these results, the accuracy of the CT to detect the exact number of lung nodules was 61%. With these findings, they concluded that manual bilateral palpation was required for correct final staging by performing a complete resection of all lung metastases (M1). The importance of complete resection was already a criterion that had been established during forty years as one of the classic criteria in the selection of patients to undergo surgery (2). This impact has been reflected in the increase in publications related to this topic in subsequent years.

The classic defense of the open approach is justified by the frequent discrepancy between the number of lesions seen in the preoperative imaging tests and the final number of resected metastases. This discrepancy has been evident since the 80's but has been maintained over the years (3-5). Thus, an open approach would allow a better lung palpation and detection of possible hidden metastases in the preoperative study, offering a theoretical complete lung resection.

The discrepancy rate between the latest generation helical CT and the pathological findings after the open surgical approach, vary between 15% and 25% (6-8). Several clinical and histological factors have been related to a greater or lesser rate of discrepancies between the CT and the final pathological findings. The most frequently

reported were the number of suspicious lesions on CT, bilateral or not of the lesions, disease-free interval, tumor doubling time and certain histological types such as soft tissue sarcomas and osteosarcomas (7,9,10).

A study published in 2011 (11) concluded that CT sensitivity in patients with single pulmonary M1 of colorectal origin was 95.5%. Another study was published in 2013 (12) based on 183 patients, on whom a lung metastasectomy was performed using a thoracotomy. Patients older than 60 years, with one or two M1 of colorectal origin or a single M1 of any other origin were considered as the group with a low probability of resecting more metastases than those observed in the preoperative CT. In this defined group of patients, there was not only an additional M1 in 4.4% of patients in this defined group.

In 1986, a study was published showing the results of performing metastasectomy using median sternotomy in patients with a history of soft tissue osteosarcoma and evidence of unilateral disease on preoperative CT (5). After two-lung examination, it was shown that 38% of the patients had involvement of both lungs. However, this bilateral involvement did not affect a worse cancer prognosis. This work showed that potential hidden metastases can be addressed in a second or successive surgical procedure without compromising the patient's prognosis.

One of the first studies comparing both techniques (Thoracotomy & VATS) in prognostic terms was carried out in 2002 (13). It included patients with a single lung lesion suspected of being metastatic on CT, less than

[^] ORCID: 0000-0003-4876-2402.

3 cm. and of peripheral location. The disease-free survival (DFS) at 2 years (VATS 50% *vs.* thoracotomy 42%) and the overall survival (OS) at 2 years (VATS 67% *vs.* thoracotomy 70%) were similar in both groups. Due to the absence of significant prognostic differences, they concluded in favor of video thoracoscopy.

In a subsequent study in 2008 (14), with patients with pulmonary metastases of colorectal origin, both approaches were compared. In the bivariate analysis, between the surgical approach used and the 5-year DFS and OS, the differences pointed to a possible beneficial effect of the thoracoscopic approach (5-year DFS of 34% for VATS *vs.* 21% for thoracotomy, $P=0.064$; and a 5-year OS of 49% for VATS *vs.* 39% for thoracotomy, $P=0.047$). In the multivariate analysis, the prognostic factors related to 5-year DFS were the presence of multiple metastases (OR 1.8; 95% CI, 1.11–2.92), hilar and/or mediastinal lymph node involvement (OR 3.48; 95% CI, 1.32–9.17), while for OS, the most influential negative prognostic factors were, the size of the metastasis as a quantitative variable in millimeters (OR 1,049; 95% CI, 1,024–1,046) and the performance of a lesser resection (OR 4.24; 95% CI, 1.19–15.1).

Another study published in 2009 (15) compared the open and thoracoscopic approach in patients with metastases of sarcomatous origin, a disease often banned from video-assisted thoracoscopic surgery (VATS). The inclusion criteria considered the potential resectability according to the number and location of the suspect nodules (two or less nodules). The results were a 3-year DFS of 26% VATS *vs.* 24% thoracotomy ($P=0.54$) and a 5-year OS of 52% VATS *vs.* 34% thoracotomy ($P=0.20$).

Over time, different studies have appeared to compare the two types of approach; most of them in selected patients, have not found any differences, and therefore conclude in favor of the video-thoracoscopic approach (16–19). With the progressive improvement of radiological technology (especially CT) in the preoperative study of metastatic disease, much more reliable progress has been made in detecting suspected lung nodules (20–25). This technological boost, together with the postoperative benefits demonstrated by minimally invasive surgery (26–29) at the expense of less pain, faster recovery, less immunological impact, better tolerance to adjuvant cancer treatments, less technical difficulty in the case of remastectomy... has been reflected in greater reliability in the use of the videothoracoscopic approach.

Although VATS surgery is one of the pillars of resection of the pulmonary nodule with diagnostic tool and/or

curative intention, sometimes the main problem that the surgeon may encounter is locating these nodules, either due to their small size or their location (30). For this reason, different preoperative location methods have been developed. These localization techniques can be categorized into 5 groups according to the materials used; simple digital palpation through the assistance thoracotomy; localization with metallic materials: hook-wire (31–34), microcoil (35,36), or spiral coil; localization with dye: methylene blue (37–39), India ink (40) or indigo carmine (41,42); localization with contrast agents: lipiodol (41–43), barium (44), or (45); radioguided occult lesion localization (ROLL) with radiotracers (46–49). Other systems used are: image-guided video-assisted thoracoscopic surgery (iVATS) (50,51) and virtual-assisted lung mapping (VAL-MAP) has evolved from bronchoscopic dye localization (52–54).

An optimal method of preoperative localization for this type of pulmonary nodules has not yet been established. A systematic review of three methods of localizing lung nodules for VATS was recently conducted (55): wire-hook localization, microcoil localization, and with lipiodol. The resulting meta-analysis aimed to compare the success rates and complications associated with these three different localization methods. The success rates between the different localization methods were similar. However, the location by wire-hook posed the problem of migration or displacement of the device, although it is true that many times the insertion area could be “marked” by the bruise produced by the harpoon. The localization method based on Lipiodol obtained the highest overall success rate: hook-wire 0.94 (95% CI, 0.91–0.96), microcoil 0.97 (95% CI, 0.95–0.98), and lipiodol 0.99 (95% CI, 0.98–1.00). The microcoil localization method found the lowest complication rates. The pneumothorax rate produced by the microcoil was 0.16 (95% CI, 0.07–0.34), by the wire hook was 0.35 (95% CI, 0.28–0.43) and by the lipiodol was 0.31 (95% CI, 0.20–0.46). The pulmonary hemorrhage rate was 0.06 (95% CI, 0.03–0.11), 0.16 (95% CI, 0.11–0.23) and 0.12 (95% CI, 0.05–0.23), respectively.

One study, based on a meta-analysis of preoperative bronchoscopic marking for lung nodules (56), included 25 studies (15 studies on dye marking under electromagnetic bronchoscopic navigation, 4 studies on assisted virtual lung mapping, and 7 others using other marking methods). The complete resection rate was 1.00 (95% CI, 1.00–1.00) while the successful marking rate was 0.97 (95% CI, 0.95–0.99). The overall rates of pleural injury were 0.02 (95% CI, 0.01–0.05) and lung parenchymal hemorrhage 0.00 (95%

CI, 0.00–0.00).

The presence of metastatic involved lymph nodes discovered during pulmonary metastasectomy has been found to negatively affect survival in patients sometimes undergoing curative intent pulmonary surgery. Therefore, a complete mediastinal lymphadenectomy, or at least lymph node sampling of various lymph node stations, is recommended at the time of pulmonary metastasectomy to complete the surgery and help define the patient's prognosis and propose future adjuvant treatment (57-62).

Classically, in a lung metastasectomy, surgeons should detect complete resection of lung lesions with negative margins, but should minimize the resection of functional lung tissue as much as possible, because of possible current or future lesions (63). They should be resected while leaving patients with adequate lung function. However, local recurrence at the surgical margin is a problem with limited wedge resections.

More than 50% of patients who undergo pulmonary metastasectomy will have a recurrence locally. This recurrence will appear 28% of the time on the surgical margin. These high percentages occur despite the fact that a complete resection has been histologically confirmed in 95% of the cases, which means that the surgical margin was free of disease (64). Pathologically, there is an increased risk of local recurrence in those patients who, although they present a disease-free surgical margin, 10 or more aerogenic diseases were observed with groups of floating cancer cells around the main tumor ($P=0.02$). Of course, the risk of local recurrence increased in those patients who presented a positive malignant surgical margin ($P=0.04$).

The existence of metastatic cells around metastases of colorectal origin is known. These satellite tumor cells represent a potential source of recurrence at the local level. For this reason, efforts should be made to maintain a distance of at least 3 mm in small nodules and at least 8-10 mm in larger sizes in order to prevent future local recurrence (65).

In another published study (66), it was shown that in surgically removed colorectal lung metastases, technical factors related to margin length and tumor size are associated with an increased risk of local recurrence. The risk of local recurrence at 2 and 5 years was 11.8% (95% CI, 8.9–14.6%) and 20.6% (95% CI, 16.2–24.8%), respectively, for each resected nodule. A greater margin of surgical resection represented a lower risk of local recurrence (HR 0.434 for each additional cm; $P=0.015$). However, a larger size in the metastasis was resected, representing a higher

risk of local recurrence (HR 1.520 for each cm of size). Thus, the risk of local recurrence was decreased in larger tumors the greater the margin of surgical resection. The tumor grade or the presence of KRAS did not represent an increased risk of recurrence locally.

Other study published in 2020 (67) where the patients were divided into three groups according to the resection margin distance from the tumor: (I) ≥ 2 cm; (II) < 2 and ≥ 1 cm; (III) < 1 cm. The OS was significantly different between the three groups ($P=0.020$). Univariate and multivariate analyses showed that a narrow resection margin was an independent prognostic factor of worse survival ($P=0.006$ and HR 3.4, $P=0.009$).

In a study published in 2009 (68), patients who did not undergo anatomic lung resection show worse survival, the argument made seems to be related to a more anatomical resection, combined with a hilar lymphadenectomy, which is capable of eliminating the spread of hidden hematogenous of colorectal cancer in the same lobe. Another study demonstrated that the morphological characteristics of the aerogenic spread with groups of floating cancer cells, associated with a vascular invasion at the metastatic site, are two prognostic factors in patients who have undergone a metastasectomy for lung disease of colorectal origin (69). Another study showed that patients whose recurrent sites extended downstream from the lung via hematogenous colorectal cancer spread, pulmonary tumor size was significantly larger than in those with recurrent sites confined to the lung and regions upstream from the lung (70). In our study published in 2016 (71), major anatomic resection was associated with a significant differences in DSS in favor of major resection *vs.* lesser resection (DSS median not reached *vs.* 52.2 months, 95% CI, 45.9–58.5, $P=0.03$) (figure 2). Also, differences in DFS were statistically significant in favor of the major resection group (DFS median not reached *vs.* 23.9 months, 95% CI, 19.2–28.6, $P<0.001$). The surgical approach (VATS versus open surgical resection) had no effect on outcome.

The evidence for pulmonary metastasectomy does not include randomized trials, the survival benefit obtained is only based on case series with selected patients. In March 2010, a randomized trial called Colorectal Cancer Lung Metastasectomy (PulMiCC) was performed. The aims of the PulMiCC study are to examine whether surgical resection of lung metastases from colorectal cancer prolonged survival and to systematically record the harm and benefits of such surgery and quality of life (72). The study was stopped due to low recruitment (65 patients). The small number of trial

participants prevents a conclusive answer to the research question. The estimated survival in this study was 38% (23–62%) for patients with metastasectomy and 29% (16–52%) in well matched controls (73).

Currently, lung metastasectomy is a widely established surgical practice in a Thoracic Surgery Department. The latest studies show a similar survival prognosis between open- and video-assisted thoracoscopic approach in selected cases, which is why the latter may have a preference given the immediate advantages of a less invasive approach (74). Despite the fact that sparing parenchymal surgery is widely established, randomized studies should define the role of anatomical resections (anatomical segmentectomy and lobectomy) in this type of pathology nowadays. There are less doubts in the role of lymph node involvement as a prognostic factor, and therefore, the need to perform a lymphadenectomy that provides us with this histopathological information. There are numerous techniques to help in the correct location and subsequent resection of suspicious lung nodules that appeared in the preoperative study and that should be resected.

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