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Pulmonary Metastases: Surgical Principles, Surgical Indications, and Innovations

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Abstract: Pulmonary metastasectomy is an established treatment that can provide improved long-term survival for patients with metastatic tumor(s) in the lung. In this chapter, we discuss the state-of-the-art thoracic surgery in surgical management of lung metastases. The principles of pulmonary metastasectomy, followed by a comparison between thoracotomy and mini-invasive surgery are presented. Different surgical indications, and oncological outcomes according to the surgical approach (open vs mini-invasive), histological types and the number of metastatic nodules in the lung are discussed. Finally, the role of surgical margin, lymphadenectomy, and surgical resection of recurrent metastases along with a brief overview of the future perspectives in thoracic surgery in the treatment of lung metastases are presented.

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INTRODUCTION

Approximately 30% of patients with a malignant disease will develop pulmonary metastases (1). Carcinoma of the colon and rectum, kidney, breast, prostate, and oropharynx are often the causes of the lung metastases. Additionally, chorionic carcinoma, osteosarcoma, soft tissue sarcoma, testicular tumors, Ewing sarcoma and thyroid carcinoma metastasize preferentially to the lungs (2). Pulmonary metastasectomy (PM) is an established treatment that can provide improved long-term survival for patients with metastatic lung cancer originating from a range of primary solid tumors. Surgery is generally proposed in cases of oligometastatic stage, and in all patients who can tolerate a surgery (3). In 1997, a long-term prognostic analysis of 5,206 lung metastasectomies showed that survival after complete resection was 36%, 26% and 22% at 5, 10, and 15 years, respectively, with a median survival of 35 months. Based on these findings, surgical resection for pulmonary metastasis has been commonly introduced in thoracic surgery (4). According to a recent report by the Committee for Scientific Affairs of the Japanese Association for Thoracic Surgery, PM accounted for 10.2 % of all entry cases of general thoracic surgery, and its use is increasing year by year (5). Thus, currently, the surgery of metastatic lung disease represents a very significant portion of the activity of a thoracic surgery department.

In this chapter, we discuss the state-of-the-art of thoracic surgery in the management of lung metastases. We start describing the principles of surgical therapy that should remain the cornerstones of lung metastases treatment: radical surgery with free margins, and adequate lymphadenectomy. We then focus on the surgical approach (open vs. mini-invasive), different oncological results according to the histological type and the number of lung metastases, and the opportunity to re-do PM. Finally, we conclude the chapter with a brief overview of the future perspectives in thoracic surgery in the treatment of lung metastases.

PRINCIPLES OF PULMONARY METASTASECTOMY

The first reported case of PM was for treating a lung metastatic lesion of renal origin (6). Since then, several cases have been reported in the literature. This type of surgery was initially evaluated in patients with tumors of various origins and based on retrospectives case series data, surgical criteria have been proposed. The accepted criteria were: (i) the surgery is low-risk to the patient; (ii) the primary neoplasm is controlled; (iii) there are no other extrapulmonary metastases; and (iv) the lung lesions appear to be completely resectable (7). In 2019, the Society of Thoracic Surgeons (STS) Work Force of Evidence Based Surgery established that some general criteria should always be observed before referring patients to metastasectomy. The most important are: (i) primary cancer control; (ii) absence of other extra-thoracic metastases; and (iii) complete

metastasis resection (8). Although substantial agreement exists among surgeons on these criteria for performing a surgery, there are no official guidelines defining the optimal surgical approach and type of resection, or whether perioperative lymph node evaluation should be performed for these patients (9). However, all patients affected by lung metastases scheduled for a surgical resection must be treated according to rigorous principles and each surgical indication should be considered on a case-by-case basis during the team's multidisciplinary and individualized discussion.

The main goal of PM is to achieve a complete resection of the metastases while preserving as much pulmonary parenchyma as possible. The goal of radical resection is generally obtained through wedge resections or surgical excision by electrocautery or laser ablation of peripheral lesions. Conversely, anatomical resection such as segmentectomy, lobectomy or pneumonectomy may be necessary to ensure radical resection of central lesions. The data published by the International Registry of Lung Metastases in 1996 allow to understand the surgical activity of different centers in Europe and North America regarding surgical PM. It was performed by wedge resection in 67% of cases, segmentectomy in 9%, lobectomy in 21%, and pneumonectomy in 3% (4). These data are comparable to those reported by a recent analysis of current surgical practice outcomes of PM, based on European Society of Thoracic Surgeons database. This database, which includes information submitted by 270 European units from 25 countries, represents a good overview of the current European surgical practices, confirming that the most common surgical resection was managed by wedge or local excision in 61% of cases. Anatomical resection was performed in 39% of cases with lobectomy, 26% of cases with segmentectomy, 1% of cases with bilobectomy, and 1% of cases with pneumonectomy (9). The cited data from two large series analyzed at two different times confirm that the trend in the frequency of surgery does not appear to have changed much over time with the majority of lung metastatic lesions located at the periphery of the lung, and easily accessible to wedge resection.

On the other hand, pneumonectomy to accomplish PM is not recommended except in carefully selected patients undergoing multidisciplinary team management. Thus, it is not a coincidence that the rate of performed pneumonectomy decreased from 3% (4) to 1% in the last decades (9). Probably this reduction is the confirmation that it is generally agreed among surgeons that this type of resection should only be kept as the last resort for metastasectomy in highly selected patients considering that it massively impairs respiratory functions. In conclusion, a pneumonectomy should be exclusively performed in highly selected patients and for very clear surgical and medical indications (9). Several considerations should be given with regards to the choice of the surgical approach (open surgery vs mini-invasive), the surgical margins to be respected, the opportunity to perform a lymphadenectomy during surgery, the histological type and number of lung metastases, and the possibility to repeat metastasectomy.

THORACOTOMY VS MINI-INVASIVE SURGERY

Traditionally, thoracotomy with manual palpation has been proposed as the standard surgical approach for performing PM. The possibility of performing a

bimanual palpation of the entire lung surface during surgery has always been considered a main advantage in avoiding missing nodules that would have remained undetected during preoperative radiological examinations. Hence, historically, the manual palpation has been proposed as a requirement to "find" all the metastases when small and multiple nodules are present on radiographic studies.

In recent years, minimally invasive approaches for lung cancer management have gained increasing acceptance, and radiological imaging has considerably improved. Thus, video-assisted thoracic surgery (VATS) has been progressively and largely adopted for performing PM procedures too. However, the utility of VATS for treating pulmonary metastases remains unclear. The main problem remains that the palpation for pulmonary metastasis is sometimes difficult or impossible during VATS. Finger palpation through port sites or utility incisions as well as indirect palpation of the lung using instruments, such as a ring forceps, can aid in finding lesions using minimally invasive thoracoscopic techniques, but close attention to the CT scan and the anatomy of the lung in real-time is as valuable. Additionally, several studies report that small or minute non-imaged lung nodules can be missed during surgery. For example, non-imaged malignant pulmonary metastases were detected in 36% of PMs performed by an open approach, which affords bimanual palpation of the entire lung (10). More recently, Cerfolio et al. discovered non-imaged malignant pulmonary metastases in 18% of patients during metastasectomy via open thoracotomy (11). At the same time, it concludes that the clinical impact of these findings is unknown, and a prospective study to further examine this issue is underway (11).

An interesting prospective observer-blinded study concerning this problem on PM has been recently reported. Eligible patients with oligometastatic pulmonary disease on computed tomography (CT) underwent high-definition VATS, with digital palpation by one surgical team and subsequent immediate thoracotomy during the same anesthesia by a different surgical team, with bimanual palpation and resection of all palpable nodules. In this study conducted on a series of 89 patients, 67 additional and unexpected nodules were identified: 22 were metastases (33%), 43 (64%) were benign lesions, and 2 (3%) were primary lung cancers. The authors concluded that a substantial number of additional nodules were detected during thoracotomy, despite advancements in CT imaging and VATS technology, and many of these nodules were malignant and would have been lost if VATS had been used exclusively. Consequently, they considered VATS inadequate if the intention was to resect all pulmonary metastases during surgery (12). On the other hand, Nakas et al. reported that DFS did not appear to be affected by the approach, at least for colorectal metastases. In their experience, VATS metastasectomy was not inferior compared to open PM because of the ability of CT to detect lung small nodules (13). Finally, many studies have shown that overall survival and recurrence survival did not differ between VATS and open PM independently of the type of metastatic primary tumor (14–16). A mini review, based on retrospective data, concluded that all thoracoscopic resections compared to open surgery were associated with better short-term outcomes, shorter hospital stays and chest drainage duration, and fewer perioperative complications (17). Furthermore, no survival differences were identified with either approach (17).

Other additional advantages of VATS have been reported in literature and are noteworthy. According to Carballo et al., the use of VATS in performing PM did

not lead to an increase in number of thoracic recurrences, keeping recurrence-free survival comparable to open PM (18). Another advantage of VATS in performing PM is the reduced invasiveness in treating patients that probably will be submitted to surgery many times. The main advantage of VATS in managing these cases would be the reduction of pleural adhesion. Furthermore, the possibility to perform a hybrid metastasectomy technique involving a combination of VATS and mini-thoracotomy or hand-assisted thoracoscopic surgery (HATS) has been developed to overcome the disadvantages of VATS PM (19). Thus, it is not surprising that in Japan more than 70% of PM procedures are performed using VATS and the frequency of such procedures is increasing year-by-year (5). In Europe, the rate of VATS procedures significantly increased from 15% in 2007 to 58% in 2018 as reported by ESTS (9).

In conclusion, the recommendation of expert consensus document on PM is that in oncological and medically appropriate patients, PM can be considered with a preference for mini-invasive surgery owing to the shortened postoperative recovery and reduced effect on short-term quality of life. If the goals of R0 and pulmonary parenchymal sparing are not achievable with mini-invasive surgery but lend themselves to open approaches (thoracotomy, sternotomy, or clamshell), open techniques are appropriate (8).

SURGICAL MARGIN

Staplers, electric scissors, laser scissors, and coagulation instruments are common devices used in performing PM (20). Regardless of the surgical device adopted, postoperative local recurrence at the surgical margin remains an important problem (21, 22). The local recurrence rate of the surgical margin varies from 4–31% after PM procedures (23–25). Surgical margin distance is recognized as a critical point of wedge resection. The relevance of margin distance is highlighted by several studies comparing the frequency of recurrence at the surgical margin after wedge resection or segmentectomy for lung metastases. Segmentectomy is known to achieve larger surgical margin than wedge resection. Lung metastases from colorectal cancer surgical margin recurrence rates were 2% with segmentectomy, and 7.3% with wedge resection (26).

In clinical practice, tumor-free surgical margin is checked macroscopically and, if necessary, by histological examinations of frozen sections. Although the surgical margin appears macroscopically to be sufficient, about 10% of the resections may be microscopically incomplete (3). To prevent local recurrence, Rusch (3) advised removing a cone-shaped pulmonary parenchyma wedge circumferentially around the nodule and to take a 0.5- to 1.0-cm margin of normal lung tissue with it in all directions. This recommendation was based on a case series with local recurrences (3). In addition, significant increases in local recurrence were found in cases of resected pulmonary metastases with a surgical margin distance of less than 7 mm (27). Indeed, satellite cancer cells, a potential source for local recurrence, are found in large numbers around colorectal lung metastasis. In a study of patients with pulmonary metastases from colorectal cancer, satellite cancer cells were identified in 99.7% of nodules within 7.4 mm of the tumor (28). Therefore, several authors suggest avoiding such failure, a wedge resection with a

sufficient margin, 10 or 20 mm, if possible (28–29). Other factors influencing surgical margins and a possible local recurrence are the size and tumor location. A recent study demonstrated that larger metastatic tumors had a higher risk of local recurrence (30). Depending on the tumor size, the safety margins may need to be increased. For these reasons, increasing importance is given to tumor/margin ratio. In a recent study, both distance from the surgical margin and tumor/margin ratio were risk factors for local recurrence and the authors concluded that margin distance should be more than 10 mm, and the tumor/margin ratio should be less than 1.7 with wedge resection for pulmonary metastases. These data confirm that tumor depth, usually evaluated by chest CT, are significantly correlated with greater local recurrence (30).

Tumor location would also play an important role in preventing recurrence at the surgical margin considering that the achievement of a sufficient surgical margin depends on tumor location. Sawabata (31) showed differential margin distances obtained with wedge resection of the tumor carried out with surgical stapling devices at different parts of the lung. In the case of tumors located in the edge of the lung, e.g., lingular segment, a sufficient surgical margin could be obtained. Conversely, in the case of tumors located in the large ovoid face, e.g., basal segment, a sufficient surgical margin could not be obtained (31). Shiono et al. suggested wedge resection for peripheral lung nodules and segmentectomy for more central lesions (32).

Finally, it has been reported that the incidence of local failure at the surgical margin is higher after PM for metastases from colorectal cancer than after PM for metastases from other malignancies (30). However, even if colorectal cancer lung metastasis shows a high recurrence rate after resection, about 28% of these patients had recurrent pulmonary metastasectomies. Therefore, a balance is needed between adequate resection for preventing recurrence and limited resection to preserve pulmonary function for a possible additional pulmonary resection (30).

LYMPHADENECTOMY

In patients with lung metastases from an extrathoracic solid organ, intrathoracic lymph nodes (LN) involvement is a poor prognostic indicator (33). Historically, thoracic surgeons rarely perform mediastinal LN dissection in the setting of metastatic disease. According to IRLM data in 1997, mediastinal LN sampling was evaluated in only 4.6% of patients (4). Since 1997, many surgeons have performed LN assessment during surgery, but this attitude remained discretional, and systematic mediastinal lymphadenectomy remains controversial. A survey by the European Society of Thoracic Surgeons in 2008 showed that 55% of surgeon have performed routinely a sample of mediastinal nodes at the time of metastasectomy, while 33% avoided nodal dissection (34). Similar percentage has been reported in more recent ESTS document published in 2021 with a LN assessment realized in 58% of patients (sampling: 21%, complete dissection: 37%) (9). Although current evidence suggests that intrathoracic LN status is an important predictor in PM, there are no randomized data that show mediastinal lymphadenectomy having a therapeutic effect. Thus, the systematic assessment of LN has historically not been widespread (34) and it is controversial whether patients with positive nodes

should be excluded from pulmonary metastasectomy (35). However, in a recent cross-sectional survey, both preoperative tissue assessment of radiologically suspicious lymph nodes and intra-operative assessment are 'recommended' by the expert panel (36). Furthermore, the recommendation of expert consensus on PM is that LN sampling/dissection concomitant with PM should be considered because pulmonary metastasis accompanied by mediastinal LN metastasis predicts poor survival (8).

SURGERY ACCORDING TO THE HISTOLOGICAL TYPE

Since each histological type behaves differently, it is reasonable to assume that the efficacy and role of surgery depends on the primary tumor histology. Regardless of histological type, several prognostic factors have been described as predictors of a worse prognosis, such as, incomplete resection, number and the size of resected tumor, LN metastases and a short DFI (disease-free interval). Conversely other predictors are specific to certain histological type.

To date, PM is considered a potentially curative treatment for patients affected by metastatic sarcoma (37). The 5-year overall survival rates after resection ranges from 15% to 50.9% (38). In a high-volume referral center, PM for sarcoma was associated with satisfactory 3 years overall survival according to the histological type: 21.4% for high risk (myxofibrosarcoma, malignant peripheral nerve sheath tumor, and Ewing sarcoma), 45.7%: for intermediate risk (leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma) and 74.1% for low risk (synovial and chondrosarcoma) neoplasm (39). The most common negative prognostic factor reported are high-risk histology, grade 3 (G3) sarcoma and the bilaterality of lung metastases (39).

Colorectal cancer is the most common primary tumor in patients who undergo PM. Similar to metastatic sarcoma, scientific evidence derived by several studies confirm that colorectal carcinoma is a favorable histological subtype for metastasectomy (40–41). Several case series in the following years confirmed this and reported excellent 5-year survival rates, with some studies reporting rates up to 68% at 5 years (42). Many prognostic factors for colorectal cancer after PM have been reported in literature over the past decades. In recent years, survival after PM in patients with colorectal cancer has improved remarkably, probably as a consequence of the positive impact of the new chemotherapy regimens. The most common poor prognostic factors reported in literature are tumor number, tumor size, LN metastases, preoperative serum carcinoembryonic antigen (CEA) level, patient >70 years old, a DFI of less than 2 years and the extrathoracic metastatic lesions treated radically before PM resection (43–44). Another interesting prognostic factor seems to be the location of primary colorectal cancer. Several studies have reported different outcomes after PM performed for colon and rectal cancer. In particular, the reported 3-year and 5-year DFS was poorer in the rectal cancer group compared to the colon cancer group (45–46). However, in these studies, no difference in OS rates has been identified between colon and rectal cancers. Similar to sarcoma and colorectal carcinoma, renal cell carcinoma, melanoma, gynecological cancer, and head and neck carcinomas are generally considered favorable for resection.

Renal cell carcinoma is the second-most common primary tumor in patients undergoing PM. Incomplete resection, high number, or large size of metastases and a short DFI are the most common prognostic factors associated with worse overall survival reported by most recent studies (47). Innovations in the field of immunotherapy and molecular-targeted therapy probably will change oncological results in the future. Less favorable evidence is reported for resected metastases of head and neck carcinomas (48). The 5-year overall survival rates after PM in this histological type ranges from 20.9% to 59.4% (49). Squamous cell carcinoma is the most common histological type of head and neck cancer. Compared to head and neck squamous cell carcinoma, adenoid cystic carcinomas have been associated with a better prognosis (50). Incomplete resection, short DFI, old age, and local recurrence before lung metastases have been reported as factors associated to a worse prognosis and poor overall survival (51). In the field of gynecological cancer, several studies have reported a 5 and 10-year survival of 40.9% and 31.4%, respectively, after PM (52). The most common factor predictive of poor survival is a short DFI, cervix primary lesion, and a large number of metastases.

Finally, with regard to breast cancer, the increase in life expectancy in patients with pulmonary metastases is mainly based on chemotherapy and anti-hormonal treatment. Therefore, in case of confirmed pulmonary metastases, the level of evidence for a curative approach is low, and a less favoritism to PM is most likely due to the improvement of systemic therapies effectively prolonging life (53).

SURGERY BASED ON THE NUMBER OF LUNG METASTASES

The number of metastatic lesions discovered before or at operation is a well-studied and important prognostic variable (54). Most authors would agree that a larger number of lesions are associated with a poor prognosis, but the cut-off value for denying PM for patients with multiple LM is undetermined. From the analysis of data in the International Registry, Pastorino et al. concluded that the number of metastases was highly significant and that patients with three or more metastases had a 33% higher relative risk of death at 5 years (4). The importance of the number of metastases has also been studied in various histological subgroups, and Girard et al. reported that the prognostic value of the number of metastases is greater for patients with a carcinoma than for those with sarcoma (55). In conclusion, the presence of more than one metastatic lesion is not always a contraindication for PM, and it seems unfair to reject PM for patients with two to four lesions (54).

RE-DO SURGERY

Resection of recurrent metastases should be considered within a multidisciplinary team and carefully individualized to define whether repeat resection is indicated. The surgical indications for repeated PM do not differ from those for the initial operation, but preoperative evaluations should be performed more carefully to ensure a complete surgical resection while maintaining physical function (56–58).

Several factors such as DFI, overall prognosis, expected benefit of medical treatment, and the patient's symptoms should be considered in decision-making. Usually, a longer time interval between the first metastasectomy and the appearance of recurring metastases appears to be prognostically more favorable. On the other side, with subsequent recurrences, DFI tends to shorten, symptoms worsen, and the value of medical treatment is lower. The cure is highly unlikely in these situations, and palliation with prolonged survival are the desired goals for treatment. The International Registry shows a startling 10% survival benefit at 5 years if a patient qualifies for a repeat PM (4). Jaklitsch and co-authors demonstrated for various primary tumors that patients undergoing one recurrent metastasectomy achieved a median survival time of more than 60 months; with two recurrent metastasectomies, median survivals were 34.7 months, and with three or more, it was 45.6 months. Patients in whom further surgery appeared impossible had a median survival of 8 months (59). It is certainly true that all patients who fulfill the metastasectomy criteria twice represent a highly selected subgroup with relatively indolent tumors. Nevertheless, aggressive repeat PMs are warranted for appropriate patients with reasonable expectations of long-term survival (60–61). Usually, repeated PM for metachronous pulmonary metastases is mainly performed in patients with colorectal cancer, renal cell carcinoma, or bone/soft tissue sarcoma, etc. (61–62). Finally, if the surgical indication for metastatic lung tumor is satisfactory and the prognostic factors such as long DFI or a small number of recurrences are met, re-surgery should be actively considered, and the significance of lung metastasectomy remains even though the drug therapy is now advanced.

INNOVATION AND FUTURE PERSPECTIVE IN THORACIC SURGERY

Several innovations have been recently introduced in the field of PM such as the radial stapler, the use of intraoperative NIR (near infrared spectroscopy) imaging, and laser-assisted surgery. The availability of new drugs and experimental surgical techniques contribute equally to this innovation process. The radial stapler seems to be an underutilized technology in thoracic surgery considering that there are few publications describing its use in thoracic surgery. Compared to a linear stapler-only option, the radial stapler may help thoracic surgeons preserve lung parenchyma during wedge resections while maintaining adequate margins (63).

Fluorescence is a new technology which has evolved concurrently with minimally invasive surgery. In recent years, new optical system has been created and commonly adopted during VATS and robotic-assisted thoracoscopic surgery (RATS). This device has been used in fluorescence-guided surgery by intravenous administration of indocyanine green (ICG) allowing an identification of the intersegmental plane in anatomical lung segmentectomies (64). Recently the use of NIR intraoperative imaging with indocyanine green (5 mg/kg and 24 hours before surgery) has been reported as useful tool in localizing known sarcoma pulmonary metastases and identifying otherwise occult lesions (65). This approach has been described in performing thoracoscopic PM of hepatocellular carcinoma

metastases by simplifying tumor locations and ensuring resection margins (66). Therefore, this approach can be a useful intraoperative adjuvant to improve PM.

Laser-assisted surgery (LAS) is a recent innovation that has been advocated especially in patients with multiple lung metastases. It is considered a promising method for PM having the advantages to allow a complete resection of a significantly higher number of metastases compared to stapling resections and to be a tissue-saving technique allowing repeated resections in case of recurrence. However, there are hardly any studies comparing surgical outcomes after laser-assisted and conventional resection and we are waiting new and lager data concerning this apparently safe technique (67–68).

Recently, experimental surgical techniques such as isolated lung perfusion with melphalan have shown promising results for unresectable metastatic colorectal cancer in animals, and phase I and II studies in patients affected by resectable pulmonary metastases from colorectal cancer, osteosarcoma, and soft-tissue sarcoma (69-70). Finally, future developments in minimally invasive approaches such as RATS and systemic treatments are likely to change the landscape and treatment guidelines for patients with metastatic lung disease.

CONCLUSION

Several take home messages should derive form this chapter. Pulmonary metastasectomy is a well-recognized and established treatment that can provide improved long- term survival for patients with metastatic tumor(s) in the lung. It should be performed according to rigorous principles and each surgical indication should be considered on a case-by-case basis during multidisciplinary team discussion and carefully individualized. Wedge resection is the most common procedure performed allowing to satisfy the main goal of pulmonary metastasectomy, which is, to achieve a complete resection of the metastases while preserving as much pulmonary parenchyma as possible. An anatomical resection such as segmentectomy, lobectomy or pneumonectomy may be necessary to ensure radical resection of central lesions. Even though open thoracotomy has been considered the gold standard procedure for a long time, the major part of PM is performed by mini-invasive surgery allowing several advantages compared to open lobectomy (less pain, shorter postoperative recovery time, and better quality of life) and maintaining R0 resection. Adequate intra-operative lymph node sampling should be considered as fundamental part of PM considering the known importance of LN involvement in determining a worse prognosis. Incomplete resection, the number and the size of resected tumor, the presence of LN metastases and a short DFI are all prognostic factors of worse survival independently of histological type. Several innovations have been introduced and probably will change the landscape and treatment guidelines for patients with metastatic lung disease.

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