

Surgical treatment of pulmonary metastases. Review of the literature a propos of a case-series of 25 recent cases.

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ABSTRACT: Surgery is the optimal treatment for pulmonary metastases from certain extrathoracic tumors (soft tissue sarcomas, colorectal and renal cancer, breast cancer and others) which fulfill some strict criteria, such as control of the primary site, long disease free interval and absence of other extrathoracic metastases (with the exception of hepatic metastases from colorectal cancer that can be also eradicated with surgery). Prolonged survival is expected after metastasectomy (even if repeated metastasectomies are required), if the number of the metastases to be resected is low (<3), if complete eradication of the metastatic deposits can be achieved during surgery and if mediastinal lymph nodes are not involved by the tumor. Limited pulmonary resection with the form of wedge resection or enucleation or typical segmentectomy is the standard surgical intervention for pulmonary metastases. Major lung parenchyma resection such as lobectomy, bilobectomy or pneumonectomy at instances required in larger, deeply situated within the lung parenchyma, metastases. Formal thoracotomy is the access of choice, while thoracoscopic resection can be applied in selected patients with solitary, peripherally located metastases. Enucleation of the metastatic deposits can be performed using the cautery or preferably using the new generation Nd:YAG lasers. Sparing lung parenchyma is crucial during pulmonary metastasectomy.

Key Words: Pulmonary metastases, Metastasectomy, Limited pulmonary resection.

INTRODUCTION

The lung is the most common site of metastatic involvement for all invasive neoplasms that develop in the human body. Thirty to seventy percent of patients who suffer from a malignant neoplasm will develop at least one lung metastasis during the course of their disease. Metastasectomy is a quite old treatment for lung metastases. Tudor Edwards in London (1927) performed the resection of a solitary lung metastasis from sarcoma of the leg, six years after the initial leg amputation. Churchill in Boston (1933) performed a formal lobectomy for metastatic to the lung kidney carcinoma. Alfred Blalock performed in 1944 a right pneumonectomy for a lung metastasis, four years after resection of a large bowel carcinoma¹. Currently, surgical treatment is the optional treatment for lung

metastases from certain tumors which fulfill certain strict criteria.

Pathophysiology-molecular biology

The malignant cells that metastasize to the lung show the typical characteristics of uncontrollable and independent proliferation, the lack of response to inhibitory signs and resistance to apoptosis and of induction of angiogenesis. The tumor cells are released from the primary tumor after disruption of the basal lamina and the extracellular matrix, entering the venous circulation. Some tumor cells that are released in the blood-stream are trapped in the pulmonary capillary bed². A minority will penetrate the pulmonary interstitium and lead to the development of a metastatic deposit. There are three main factors that make the

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lung such a frequent metastatic site. The whole blood volume passes through the pulmonary capillary bed many times each day, the pulmonary capillary bed is the richest in the human body and finally, the high partial pressure of oxygen in the pulmonary interstitium significantly contributes to the growth and development of the metastasis ("seed" and "soil" theory). The tumor cells can also reach the lung through the lymphatic system³.

The tumors that tend to more frequently metastasize to the lung are choriocarcinoma, Ewing sarcoma, malignant melanoma and osteosarcoma. Since they are not usual themselves, lung metastases usually develop from the much more frequent colorectal, breast and renal cell carcinoma³. We arrange below more information for each one of the three most frequent primary tumors that give metastases to the lung.

1. *Colorectal carcinoma*: It is the second most frequent malignant disease in the human body and is still the second cause of death from cancer among humans, despite the progress that has been made in the screening of population/early diagnosis and treatment. Although, 2/3 of the patients have potentially completely resected primary tumor, 30%-50% will develop distant metastases 2 to 3 years after colectomy⁴. Lung metastases from colon cancer usually appear to follow liver metastatic disease. In other, less frequent instances, lung metastases are diagnosed at the same time with the diagnosis of the primary tumor or develop later in the absence of liver metastases (skip metastases). The main prognostic factors after metastasectomy are:

1. Long disease free interval (DFI)
2. Carcinoembryonic antigen (CEA) < 5ng/ml before thoracotomy
3. Single isolated metastasis with diameter less than 3 cm
4. Absence of mediastinal lymphadenopathy.

Around 10% of the patients will have concurrent liver and lung metastases. The survival rate will drop to almost half in this case (40 months versus 87 months if liver metastases don't exist)⁵. The prognosis is better if the metastases are resected from both organs and aggressive treatment is also recommended in metachronous liver and pulmonary metastases^{6,7}.

2. *Breast carcinoma*: Three percent of all women with breast cancer will develop a solitary pulmonary

lesion that will be detected with plain chest radiography during the course of their disease. Thirty to forty percent of them are found to be metastases from the primary tumor. On the other, hand lung metastases are the cause of death in 25% of women with breast cancer⁸. The role of surgical treatment of lung metastases from breast cancer isn't absolutely clear because of its combination with chemotherapy and hormonal therapy⁹. Lastly, there are some indications that surgical resection of the primary tumor leads to a phenotype change of the lung metastases with increased proliferation without resistance to apoptosis¹⁰.

3. *Renal cell carcinoma*: Lungs are the most common site for metastases from renal cell carcinomas. Surgical resection appears to have positive outcome even though immunotherapy is another choice. The main prognostic factors are the number of metastases, the existence of mediastinal lymphadenopathy, the long DFI and the ability for complete resection which brings the 5-year survival rate to 45% against 8% in case of incomplete resection⁹.

General Aspects of Lung Metastasectomy

The common criteria which are used in order to select patients that would benefit from surgical treatment of their metastases are the following:

Control of the primary tumor or the possibility to be controlled.

Long DFI that is the length of time it takes for a cancer to recur once it has been considered eradicated. Longer DFIs are associated with better prognosis.

Complete resection of the metastatic tumor with preservation of adequate healthy lung parenchyma. Complete resection is associated with 38% 5-year survival, while incomplete resection drops the survival rate to 10%. The number of metastases and their precise location are also considered. For over 4 metastases the 5 year survival is 20% while for less than 3 is 40%¹¹. For unilateral or less than 3 metastases and FEV₁>80% surgical treatment is indicated. For bilateral or more than 3 metastases the decision is taken after careful consideration of all these factors.

Extrathoracic metastatic disease must be excluded¹².

Lack of alternative therapy with similar or better results than surgery.

Absolute contraindications are considered to be

mediastinal lymph node invasion, FEV₁ or DLCO < 40% of the predicted and age more than 80 years. Relative contraindications for metastasectomy are BMI > 35 kg/m² or BMI < 15 kg/m². Multiple bilateral metastases and previous lung or liver metastasectomy (in colorectal carcinomas) are not considered to be contraindications¹³. However, it is believed that the number of metastases is an absolutely negative prognostic factor because it is highly associated with the malignancy of the primary tumor and the metastasectomy will not change the course of aggressive cancers¹⁴. The preoperative detection of high levels of tumor markers is a negative prognostic factor, while men seem to have better prognosis¹⁵.

While in primary lung cancer anatomical resection is preferred, pulmonary metastases tend to be peripherally located and limited resection as wedge resection or simple enucleation of the tumor deposit with clear margins is usually adequate treatment⁹. When metastatic disease is more centrally located within the lung parenchyma, the anatomic resection (ie, segmentectomy, lobectomy, bilobectomy or even pneumonectomy) may be performed with any effort made to preserve as much pulmonary parenchyma as possible in each case¹². Pneumonectomy is required in case of a large metastasis or a metastasis critically involving pulmonary hilar structures. Resection with clear margins (R0) is associated with longer survival rates¹⁶. Extended resections (en bloc resection of lung parenchyma and chest wall, diaphragm, superior vena cava, pericardium) are accepted and can be followed by reconstruction of the resected structures¹⁷. According to the International Registry of Lung Metastases the mortality rate following extended resections is completely accepted (1.2% following lobectomy-bilobectomy and 3.2% following pneumonectomy)¹.

Repeated metastasectomies result in higher survival rate¹⁸. Repeated metastasectomies are mainly performed for metastases from colorectal cancer and sarcomas. In theory, up to 4 metastasectomies are accepted, while longer DFIs are related with 48% five-year survival rate⁹.

Concerning mediastinal lymph node invasion, thoracic surgeons don't seem to agree if lymphadenopathy will affect their decision to perform metastasectomy in a patient. In colorectal cancer with synchronous

liver metastases and in central lung metastasis it is more possible for the mediastinal lymph nodes to be affected¹⁹. Thoracic surgeons believe that hilar and mediastinal nodes should always be resected or at least sampled in order to have a more accurate prognosis. The resection lasts only 15 to 30 minutes and there is no significant raise in mortality rate¹³. A different approach is that lymph nodes should always be removed during all major lung parenchyma resections and during minor resections for pulmonary metastases from colorectal and renal cell cancer¹⁸.

Surgical treatment

Patients who suffer from extra-thoracic metastatic disease are not candidates for surgical resection of their pulmonary metastases and the first choice treatment includes systemic therapies, despite the fact that these are neither curing the patients nor prolonging survival. Preoperative or postoperative systemic therapy has no significant impact on long-term survival rate, consistent with data published elsewhere¹¹. It is widely accepted that surgical resection (metastasectomy) improves long-term survival of patients who comply the criteria for being selected for such a therapeutic approach, and thus it is considered as a significant option for pulmonary metastases. Moreover, the improved survival that follows resection of lung metastases has broadened current surgical indications and the number of patients who are chosen to be treated surgically increases continuously. Different approaches (formal thoracotomy or video-assisted thoracic surgery) and different surgical strategies are used in daily practice to perform metastasectomy.

Surgical approach

1) *Formal thoracotomy* provides the best choice for pulmonary metastasectomy. It allows palpation of the whole lung and consequently the detection of additional small metastatic deposits that are not visible on chest CT scan. Thoracotomy offers the best chance to achieve resection of larger nodules with clear margins.

2) *Video-Assisted Thoracic Surgery (VATS)* is the less invasive surgical approach in comparison to formal thoracotomy. It is widely used and it offers the benefit of low postoperative pain, faster postoperative

recovery, decreased length of hospital stay and earlier return to everyday activity. VATS resection is better suited for solitary, larger than 1cm but less than 3cm metastatic peripheral pulmonary nodules. The major reported disadvantage of VATS metastasectomy is the inability to palpate the lung and to detect other, possible metastatic, lesions during the operation²⁰.

Surgical strategies and modern instrumentation

1) *Wedge resection* of metastatic nodules using stapling devices is the most common used method to resect metastatic nodules. It provides a fast and airtight resection that is mainly suitable for peripherally located in lung parenchyma nodules. The common disadvantage of wedge resection is the amount of healthy lung parenchyma surrounding the malignant nodule that is sacrificed during this type of resection using either stapling devices or hand-sewing techniques.

2) *Enucleation* of the metastatic nodules is applied for the resection of multiple metastatic lesions or deeply situated lesions. The main advantage of enucleation is the elimination of healthy lung parenchyma to be sacrificed (lung parenchyma sparing technique) that can be crucial in patients with limited pulmonary reserve. Enucleation is also helpful when facing deep-seated lesions or nodules that are located in the broad surface of the lungs. When this technique is chosen, the lung should be inflated. The fact that the lung needs to be in an inflated state makes enucleation an unsuitable technique to be performed with VATS²¹.

Instruments for enucleation

Enucleation can be performed with different instruments the simplest of which is *cautery (electrosurgical device)*. Cautery has the disadvantage of damage of the adjacent to the nodule pulmonary parenchyma, while hemostasis and aerostasis are limited making necessary the application of multiple additional sutures. In contrary, the use of the *new generation lasers (1318-nm wavelength Nd:YAG laser, 40 watt)* for the enucleation of pulmonary metastases has three major advantages. First of all, it allows sparing as much lung tissue as possible, when resecting lesions that are deep-seated. Secondly, it causes the minimal deformity and damage of the adjacent lung tissue. Finally, when the lesion is next to a major bronchus or vessel, it is possible to dissect the maximum margin of tissue

around the lesion, without causing any injury to the adjacent major structures. The surface of the lung is simply over-sewed by a continuous suture for reapproximation of the visceral pleura in order to minimize postoperative air-leak²¹.

The LigaSure system is an electrothermal bipolar tissue sealing technique specifically used for non-anatomic, staplerless pulmonary resection. The emission of bipolar energy leads to vessel compression, which makes it easier to check the bleeding and allows local hemostasis. The experience in using this system in thoracic surgery is still limited. Surgical parameters (amount of postoperative bleeding, operating and hospitalization times) seem similar to the ones observed when resection is performed with stapler devices, but LigaSure system allows the minimal thermal damage²¹.

Ultracision scalpel (Harmonic scalpel) works by liberating energy (in the form of an ultrasonic wave) at the tip of the scalpel. The main advantage of Harmonic scalpel is the reduced lateral spreading of the heat which results in the ability to operate near vulnerable structures and the minimal smoke production²¹. *The saline-enhanced thermal sealing* helps to convert the electrical energy into thermal into the tissue. The continuous flow of saline is cooling the tissue and the peak limit temperatures are limited to 100°C or less. This differs from the conventional electro-surgical devices in which tissue temperature even exceeds 300°C. The results of the high tissue temperatures are tissue desiccation, char formation, smoke generation, electrodes sticking to tissue, and undesired lateral thermal damage. The saline-enhanced thermal sealing avoids these undesirable tissue effects, while being able to achieve sufficient hemostasis and pneumostasis of the lung tissue. This specific technique is used to perform nodulectomies and wedge resections. The coagulated vessel and bronchiole need to be individually divided and thus the operation time is more than the one needed in the conventional electrocautery or laser procedures. During the operation the lung is deflated and it is common that more than the desired functional lung tissue is finally removed. The saline-enhanced thermal sealing is used in both thoracoscopic and open procedures²¹.

We have to emphasize that all these devices (*LigaSure system, Ultracision scalpel and saline-enhanced*

thermal sealing) are not the best choice when handling with lung parenchyma resection, because of their probable inability to achieve permanent aerostasis. The need for additional deep sutures to achieve aerostasis omits their theoretical advantages to spare lung parenchyma. Late appearance of air leaks that prolongs chest tube drainage is another problem that is associated with their use in enucleation of pulmonary metastases. Laser resection and cautery still remain the standard instrumentation for the enucleation of pulmonary metastatic nodules.

Case-series of lung metastasectomies

We arrange below a retrospective review of 25 patients who underwent surgical resection of their lung metastases from different primary tumors. They were all admitted and treated in AHEPA Hospital of Thessaloniki between 2007 and 2011.

Demographic data (name, age), characteristics of the metastases (number, site, size), DFI, the type of surgical approach, levels of CEA before surgery (among patients with colorectal cancer) were recorded. The above mentioned characteristics of the 25 patients who underwent pulmonary metastasectomy are presented in Table 1.

Most of the patients were referred to the Thoracic Surgery Department from the Oncology Department after detection of a possible malignant pulmonary lesion. All patients underwent a chest HRCT in order to evaluate respectability and the size and precise location of the nodules. Their respiratory function was evaluated with spirometry.

Different types of resections were performed depending on the location of the lesion, the extent of invasion and the preoperative respiratory function, while four of them underwent repeated metastasectomies. All the 25 patients who underwent metastasectomy were evaluated in the department of clinical oncology and systemic treatment was administered by the clinical oncologists. The main results of metastasectomy appear also in Table 1.

The median DFI was quite long (24 months) while the survival rate is quite good extending up to 44 months. Wedge resection or enucleation of pulmonary metastases or combination of wedge resection and enucleation of multiple lesions was performed in 16

out of the 25 patients (64%) (Table 1). Gross involvement of the major fissure or involvement of the lung hilum made necessary pneumonectomy for eradication of the disease in two patients. Gross involvement of the minor fissure required bilobectomy (1 patient) for eradication of the tumor, while deeply situated or larger tumors (> 5cm) required lobectomy (6 patients). (Table 1).

Multiple surveys consider the level of CEA as a negative prognostic factor for patients with metastases from colorectal cancer. We were able to record the level before metastasectomy in 5 patients. Two of them had low levels of CEA (< 5ng/ml) and a single lung lesion, while the rest three had elevated CEA serum levels. One patient with elevated serum CEA levels before metastasectomy had two lung metastases, while another one underwent 3 metastasectomies due to recurrent lung metastases. Apart from that, the level of CEA obtained from three patients with history of colorectal carcinoma that are not included in the present case-series could be associated with the aggressiveness of the primary tumor (colorectal cancer). Two patients who had a single lung lesion had very low levels of CEA (< 5ng/ml). Their lesions proved to represent benign nodules after resection, while a third patient had very high serum CEA levels (111ng/ml) and suffered from simultaneous metastatic disease to the thoracic spine. From the thoracic surgeons' point of view, it would seem reasonable to always obtain a CEA serum level during the preoperative evaluation of the patient, and if it is high it seems realistic to proceed with whole body PET-CT scan²².

Table 1. Demographic data, main characteristics and results of the 25 patients who underwent pulmonary metastasectomy.

Age in years (mean, range)	65.2 (3-84)
Gender	Male: 13, Female: 12
Primary tumor site	Colorectal: 12 Breast: 3 Kidney: 3 Skin: 2 Uterus: 1 Head-Neck: 1 Liver: 1 Bladder: 1 Soft Tissue sarcoma: 1
Disease free interval in months (median and range)	24 (2-120)
Number of resected metastases (mean and range)	1.9 (1-9)
Location of metastases	Right Lung Upper Lobe: 3 Middle Lobe: 3 Lower Lobe: 5 Major fissure (involvement of 3 lobes) Minor fissure (involvement of 2 lobes) Left Lung Upper Lobe: 9 Lower Lobe: 6 Hilum: 1 Endobronchial: 1
Maximum diameter of the resected metastases in cm (mean \pm SD, range)	2.33 \pm 1.5 (0.5 – 7.0)
Type of resection	Wedge resection, enucleation or combination: 16 Lobectomy: 6 Bilobectomy: 1 Pneumonectomy: 2
Repeated metastasectomy	4 patients (1-3 metastasectomies)
Surgical approach	Formal thoracotomy: 23 VATS resection: 2
Preoperative CEA levels (ng/ml) in 5 patients with metastasis from colorectal cancer (median and range)	10.14 (1.07 – 275.5)
Follow-up after treatment in 15 out of the 25 patients	11 survivors (3-37) – median: 20.5 4 deaths (9-44) – median: 12.0

Η χειρουργική θεραπεία των πνευμονικών μεταστάσεων. Ανασκόπηση της βιβλιογραφίας και αποτελέσματα από 25 πρόσφατες περιπτώσεις.

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ΠΕΡΙΛΗΨΗ: Η χειρουργική θεραπεία είναι η αποτελεσματικότερη θεραπεία για τις πνευμονικές μεταστάσεις από συγκεκριμένους εξωθωρακικούς όγκους, όταν πληρούνται ορισμένα κριτήρια, όπως είναι ο απόλυτος έλεγχος της πρωτοπαθούς εστίας, το μεγάλο διάστημα ελεύθερο νόσου και η απουσία άλλων εξωθωρακικών μεταστάσεων (με εξαίρεση τις ηπατικές μεταστάσεις από καρκίνωμα του παχέος εντέρου και του ορθού, που μπορούν να υποβληθούν σε ριζική εκτομή). Παράταση της επιβίωσης με τη μεταστασεκτομή ή ακόμη και με επαναλαμβανόμενες μεταστασεκτομές αναμένεται σε ασθενείς που παρουσιάζουν μικρό αριθμό πνευμονικών μεταστάσεων (<3), όταν οι μεταστατικές εστίες μπορούν να αντιμετωπιστούν ριζικά με τη χειρουργική και όταν οι λεμφαδένες του μεσοθωρακίου δεν είναι προσβεβλημένοι από τη νόσο. Περιορισμένη εκτομή του πνευμονικού παρεγχύματος, με τη μορφή της σφηνοειδούς εκτομής, της εκπυρήνωσης και της τυπικής τμηματοεκτομής, αποτελεί την ιδανική χειρουργική θεραπεία για τις πνευμονικές μεταστάσεις. Μεγαλύτερες εκτομές, όπως λοβεκτομή, δилоβεκτομή ή ακόμη και πνευμονεκτομή μπορεί να απαιτηθούν σε μεγαλύτερες, βαθιά εντοπιζόμενες στο πνευμονικό παρέγχυμα μεταστάσεις. Η τυπική θωρακοτομή είναι η καλύτερη προσπέλαση, ενώ η θωρακοσκοπική αφαίρεση ενδείκνυται σε μονήρεις, επιφανειακές μεταστάσεις. Η εκπυρήνωση των πνευμονικών μεταστάσεων γίνεται με την εφαρμογή ηλεκτροδιαθερμίας ή των νέας γενιάς Nd:YAG lasers, με στόχο τη διάσωση κατά την επέμβαση όσο το δυνατό περισσότερου υγιούς πνευμονικού παρεγχύματος.

Λέξεις Κλειδιά: Πνευμονικές μεταστάσεις, Μεταστασεκτομή, Περιορισμένη εκτομή πνευμονικού παρεγχύματος.

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