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Research Article

Pulmonary Metastasectomy: Why Not?

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Abstract

Introduction: Surgical resection of pulmonary metastases was introduced as an important form of treatment for a variety of solid tumors. Several series evaluating salvage surgery for metastatic disease, showed acceptable five years survival.

Materials and Methods: Studies on pulmonary metastasectomy were identified using MEDLINE and the Cochrane Library. Studies consisted of reviews and case series were included. Entry criteria such as operative morbidity and mortality, type of resection, systemic therapy, primary tumor characteristics, disease free-interval, and pulmonary nodules aspects were considered.

Results: The results of lung metastasectomy should be analyzed from the point of view according to the critical factors that can affect survival, such as tumor histology, number of nodules and free disease interval. A limitation of this study lies in the fact that no evaluation of variables related to the biological behavior of different histological types, which may explain the evolution of clinical metastases.

Discussion: According to the principles of oncological surgery, complete removal of all pulmonary foci is associated with increased survival. The data also suggest that the preoperative radiological work-up evaluation however, has low accuracy and the intra-operative staging by experienced surgeons is essential for the resection of all metastases.

Conclusion: Pulmonary metastasectomy is a potentially curative treatment. The resecability, the disease-free interval, and the number of resected nodules, are the most important predictors of survival.

Keywords: *Pulmonary Metastasectomy; Surgical Resection; Lung Metastasectomy*

Introduction

Pulmonary metastases are the harbinger of systemic spreading of malignant tumor. Although primary tumors can be locally controlled with surgery and/or radiotherapy, the treatment of choice for metastatic disease is chemotherapy or targeted therapy. Although lung metastases often represent widespread systemic disease, selected groups of patients present with disease localized solely in the lungs, and may have distinct biological behavior. Therefore, such patients can be candidates for surgical treatment.

Surgical resection of pulmonary metastases was introduced as an important form of treatment for a variety of solid tumors [1]. Several series evaluating salvage surgery for metastatic disease, showed survival rates five years ranging from 5% to 85%, with acceptable morbidity and mortality [2]. These data are shown on table 1.

Type of tumor	Five-year overall survival after pulmonary metastasectomy
Soft tissue sarcomas	18% - 35%
Colorectal carcinomas	25% - 42%
Germ cell tumors	30% - 84%
Malignant melanoma	4% - 14%
Kidney carcinoma	13% - 55%
Breast carcinoma	14% - 36%

Table 1: *Overall survival estimated at five years in patients undergoing pulmonary metastasectomy.*

However, most studies in the medical literature reported results of pulmonary metastasectomy in a patient population typically collected over a long period of time when treatment, diagnosis and management have changed but have not resulted in any convincing conclusions. None of the prospective studies included a control group or randomization, comparing surgery with other standard systemic treatment. All data are susceptible to the limitations of retrospective analysis, and patient selection bias [3].

Aim of the Study

The aim of this study is to offer a critical analysis on this procedure, regarding its historical notes, clinical data, and surgery related survival impact.

Material and Methods

A methodological assessment of the literature where studies published in English were included.

Studies on pulmonary metastasectomy were identified using MEDLINE (January 2002 - December 2016) and the Cochrane Library (January 2002- December 2016).

The search words were: pulmonary metastasectomy, pulmonary metastases resection, surgery on pulmonary metastases, and lung metastasectomy and/or lung metastases resection.

In order to be included in this review, studies consisted of reviews and case series. Entry criteria for studies included: operative morbidity and mortality, type of resection, systemic therapy, primary tumor characteristics, disease free-interval, and pulmonary nodules aspects.

The surgical approach included unilateral or bilateral thoracotomy, median sternotomy, bilateral anterior thoracotomy and videothoracoscopy (VATS).

The author attempted to view pulmonary metastasectomy as a surgical option for patients with pulmonary nodules resected - in patients with previous tumor diagnosed- also offering a critical review of this technique.

Patient selection

The International Registry of Lung Metastases (IRLM) published in 1997, with retrospective and prospective data, experience based on 5206 patients from 18 centers in the U.S., Europe and Canada. With median follow-up of 46 months observed in patients with complete resection, they found a survival of 36% in five years, 26% in 10 years and 22% in 15 years. The survival for patients with incomplete resection was 13% in five years and 7% in ten years, with a median of 15 months [4]. Data analysis from this important study also allowed the development of a prognostic model with four groups:

- Group I: Resectable metastases, disease-free interval > 36 months and single metastases (or no risk factor);
- Group II: Resectable metastasis, free interval disease < 36 months or multiple metastases (or one risk factor);
- Group III: Unresectable metastases, disease-free interval < 36 months and multiple metastases (or two risk factors),
- Group IV: Unresectable metastases.

Thus, the prognostic factors of greatest impact were related to disease-free interval greater than 36 months, presence of a single lesion and the possibility of complete resection of the lesions. These factors predictions were tested for various types of primary tumors and were significant in each specific type. The overall survival was different for the four groups and are shown in table 2.

Group	Median survival (months)
I	61
II	34
III	24
IV	14

Table 2: *Survival according to prognostic group of the International Registry of Lung Metastases.*

Downey., *et al.* [5] emphasized the importance of surgical reexploration in patients with new pulmonary recurrence, where survival for patients operated at least twice was 42.8 months, with an estimated 36% in five years. In this series, the most important factors correlated with better survival were complete re-resection, less than three nodules resected and greater resected nodule < 2 cm ($p = 0.003$).

The selection criteria for surgical resection of lung metastases is currently considered as standard treatment in select cases, and routinely performed in specialized centers. Although the selection criteria have been expanded, it is difficult to assess the true proportion of patients who may benefit by salvage surgery, because the determinant cannot be defined in most clinical situations. In some tumors such as sarcomas and germ cell tumors, a large proportion of patients (> 50%) may be candidates for metastasectomy [5]. With regard to patients with epithelial tumors, the minority of patients may benefit from the procedure. The decision to refer the patient for surgical treatment should be multidisciplinary, and the most relevant criteria for surgical indication include:

1. Controlled or controllable primary tumor;
2. Completely resectable lesions;
3. Absence of extra-pulmonary disease;
4. Lack of effective systemic therapy;
5. Clinical condition to tolerate the planned procedure.

Still it is worth noting the presence of criteria extended or exception for patients with lung metastases in specific situations:

1. Need for diagnosis;
2. Removal of residual nodules after chemotherapy;
3. Symptomatic metastases;
4. Obtaining tissue for tumor markers and immunohistochemistry.

The current data available suggest that pulmonary metastasectomy can increase survival of patients with low morbidity and mortality, and the five-year survival ranges between 20% - 40%, figures stronger than chemotherapy or radiation therapy only [6].

Results

The results of lung metastasectomy should be analyzed from the point of view according to the critical factors that can affect survival. Such analysis results should also be grounded in reviews of primary studies in histology (breast, colon, melanoma) or in patients with similar histologies (soft tissue sarcomas) in a sufficient number of patients. Prognostic factors were reviewed in several series in order to show its influence alone or in combination for survival analysis and the description that best fits the selection criteria [7]. The results of the International Registration of Lung Metastases confirm that metastasectomy is a form of potential therapy for healing that can be safe with low mortality [4].

According to the principles of oncological surgery, complete removal of all pulmonary foci is associated with increased survival. The data also suggest that the preoperative radiological work-up evaluation however, has low accuracy and the intra-operative staging by experienced surgeons is essential for the resection of all metastases. In this context, VATS cannot provide security for the removal of all metastases [8-10].

A limitation of this study lies in the fact that no evaluation of variables related to the biological behavior of different histological types, which may explain the evolution of clinical metastases.

Currently, VATS may be indicated for the diagnosis or staging to evaluate the extent of disease, or resection of metastases in patients with single nodules in peripheral topography [10]. Complications of VATS include incomplete resection and pleural implantation after extraction of lung metastases [8,11].

The role of pulmonary metastasectomy is less evident in patients with breast tumors and melanoma, which require further definition in future prospective studies. Another area of uncertainty is based on the effectiveness of surgical staging of occult metastases by contralateral disease detected by median sternotomy - or bilateral thoracotomy - in some tumor histologies that not only sarcomas, and the actual role in the contribution of induction or adjuvant chemotherapy in some specific types of tumors [8].

Discussion

The first surgical resection of metastatic lung is credited to Weinlechner, which in 1882 as part of a surgical resection of primary tumor of the chest wall, incidentally resected metastatic pulmonary nodule as a complementary procedure. However, pulmonary resection for metastatic disease was first reported as independent procedure in the medical literature by Division in Europe in 1926 and Torek in the United States in 1930 [12]. In 1927, Tudor held in London sublobar resection for metastatic nodule from lower limb sarcoma. This patient remained alive 18 years after metastasectomy. In 1933 in North America, Barney and Churchill resected a solitary mass by lobectomy, and subsequently proven metastatic renal cell carcinoma. The patient then underwent nephrectomy to remove the primary tumor and survived disease-free for 23 years [12].

In 1947 Alexander and Haight reviewed 24 patients (16 carcinomas and 8 sarcomas) who underwent pulmonary metastasectomy, and initially discussed the selection criteria. This series also contains the first report of metachronous metastasectomy, and the patient remained disease-free 14 years after the second resection.

Interestingly at this time, the vast majority (80%) patients were submitted to lobectomy or pneumonectomy for resection of pulmonary metastasis, when rates of postoperative mortality were around 10% [12]. Simultaneous resections of multiple synchronous lung metastasis were described by Mannix in 1953. This time it was first reported resection of lesions by means of a six lingulectomies and basal segmentectomy, held in the same surgical procedure. The review of the Mayo Clinic between 1942 and 1962, based on 205 patients, highlighted the economic value of resection and the limitations of preoperative staging by Thomford., et al. In this series, the probability of survival at five years was 30%, and there were no differences between patients with single or multiple metastases [12].

In 1979, McCormack., *et al.* reported the experience of Memorial Sloan-Kettering Cancer Center through the results obtained in 402 patients and 622 thoracotomies, with very reasonable survival, according to selection criteria established in advance [12].

Pathophysiology

The spread of cancer cells with subsequent appearance of metastatic disease is the single factor of worse negative prognostic factor in cancer treatment. As an example of what happens with colorectal tumors, where overall survival is around 90% in localized disease, but in the presence of liver or lung metastases, survival drops to 10% [13].

The purpose of the follow-up of cancer patients treated thus aims to ultimately identify the development of metastases. When the tumor is locally controlled, chemotherapy can eradicate occult metastases or micrometastases. Even with the advancement of multidisciplinary treatment, however, metastatic disease remains the leading cause of mortality in patients with cancer. Determining which patients and what types of tumors have a higher risk of dissemination, is a major goal of the oncologist. The histological heterogeneity of certain tumors is related to the propensity to develop lung metastases. Thus, tumors such as soft tissues sarcomas and osteosarcomas, primarily metastasize to the lungs. In case of other tumors such as neuroblastoma and prostate, lung metastases rarely present during follow up. These observations raise some questions: 1- What causes the tumor to become metastatic? 2- Why some types of tumors have the pulmonary parenchyma as the preferred target for metastases?

Usually, malignant tumors metastasize through hematogenous routes, lymphatic, or by direct invasion. Hematogenous metastases are most often found in the lungs, liver, brain, and bones. Tumor cells that metastasize to the lungs can become trapped in the capillary endothelium, and many of these tumor emboli die. However, others survive and ultimately proliferate. Tumor cells can also be transported through capillaries and occupy a specific location in the lung or spread throughout the parenchyma (ex. lymphangitis in breast tumors).

Until the 1970s, is credited to Paget who in 1889 proposed the theory of choice of target organs by the primary tumor to metastatic cell installation. Such a theory put under the hypothesis of random dissemination cancer, the most widely accepted so far. The theory became known as the "seed and soil theory", in which the tumor would find affinity for the installation environment and proliferation in certain organs [3].

More recently, improvements in technologies of molecular biology, cellular and images, highlighted the events that occurred between the primary tumor growth and metastases of radiological appearance - also known as the cascade of metastases. Given the complexity of this process, the events within this cascade are postulated as the primary target of intervention for the prevention of distant metastases.

Symptoms

Most patients are asymptomatic at diagnosis of lung metastases. Normally the pulmonary nodules are identified during routine follow-up of the primary tumor after treatment in radiography or chest computed tomography. Respiratory symptoms such as cough and hemoptysis may be present in cases where there are hilar involvement, or bronchial invasion (Figure 1). In endobronchial metastases, there may be persistent dry cough, or massive hemoptysis. In some patients (specially in breast, melanoma and renal tumors), endobronchial metastases may cause segmental atelectasis or even of the correspondent entire lobe [3].

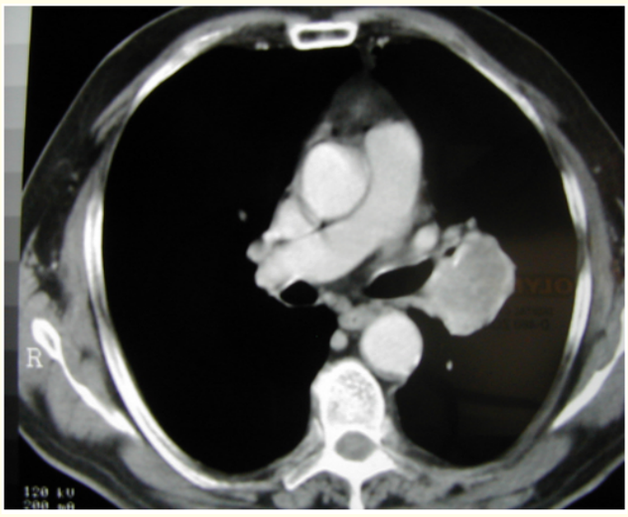

Figure 1: *Metastatic testicular tumor with invasion of hilar left bronchus.*

The peripheral location of tumors can invade the parietal pleura or chest wall, in which cases the patient usually referred chest pain. More rarely, peripheral tumors can rupture and cause pneumothorax, a fact more common in patients with sarcomas. When there are multiple nodes (or lymphangitis carcinomatosis), especially in bilateral topography, patients also may develop a dry cough or dyspnea (Figure 2).

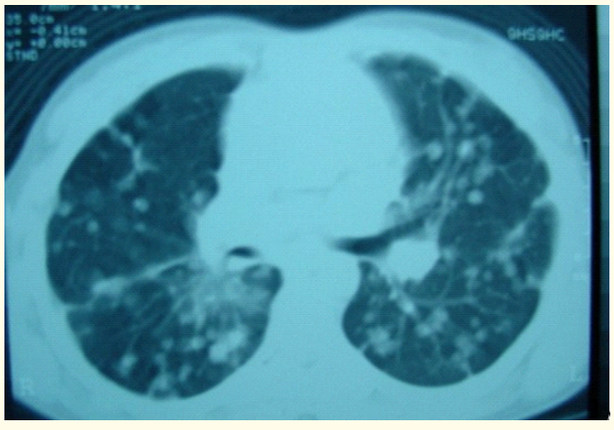

Figure 2: *Chest CT showing multiple nodules with lymphangitis in patients with breast cancer.*

Pre-Operative Evaluation

As the main objective is to assess which patients will benefit from pulmonary metastasectomy. the appropriate selection is the key to success for this procedure. The radiological evaluation is mandatory in careful pre-operative. Many times during the follow-up of cancer patients can view up to the pulmonary lesions in chest X-ray, either due to size, or due to the multiplicity of lesions (Figure 3). Anyway, there is no specific radiological finding of pulmonary metastasis, however, in patients with a history of treated tumor and present with well-circumscribed nodule(s), mainly in the lower lobe(s), should be strongly investigated in this direction (Figures 4 and 5).

Figure 3: *Plain chest radiograph of a patient with renal cell tumor and multiple bilateral lesions.*

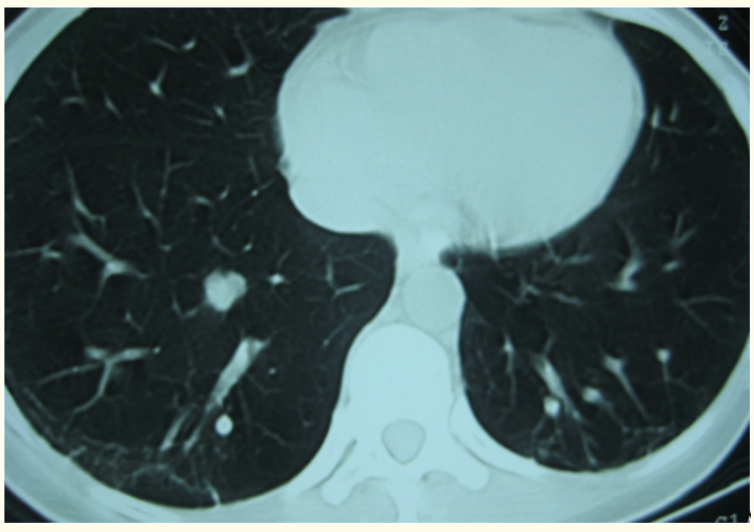

Figure 4: *Patients with soft tissue sarcoma and single metastasis in RLL*

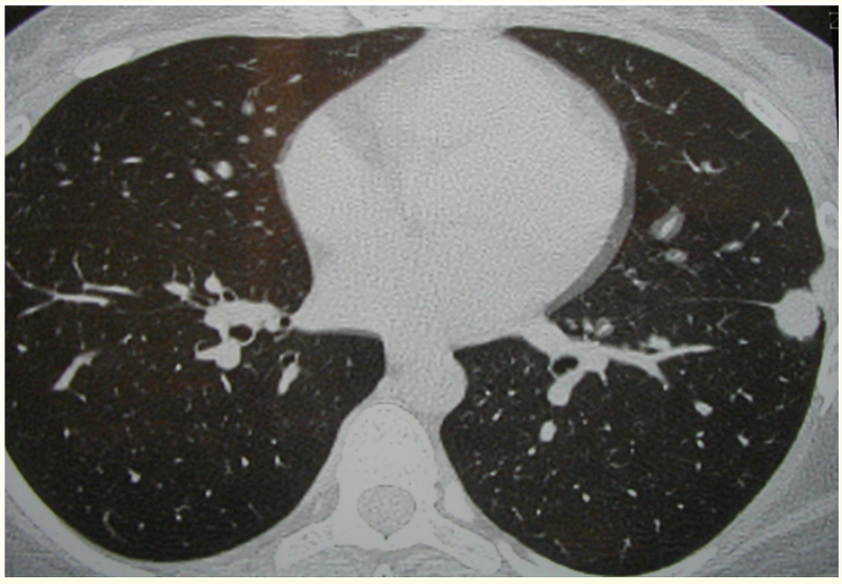

Figure 5: *Patient patients with rectal cancer and lung metastasis in the LLL*

Patients with suspected pulmonary metastasis on chest X- ray, should undergo computed tomography (CT) scan of the chest, since this test more accurately identifies the location of lesions and provides superior sensitivity by showing nodules between 2 and 4 mm - especially if helical technique is applied. In addition, helical chest CT may still show nodules not seen on chest radiography. In CT, the lung metastasis can be diagnosed as single or multiple lesions, and may still present as miliary lesions (Figures 6 and 7).

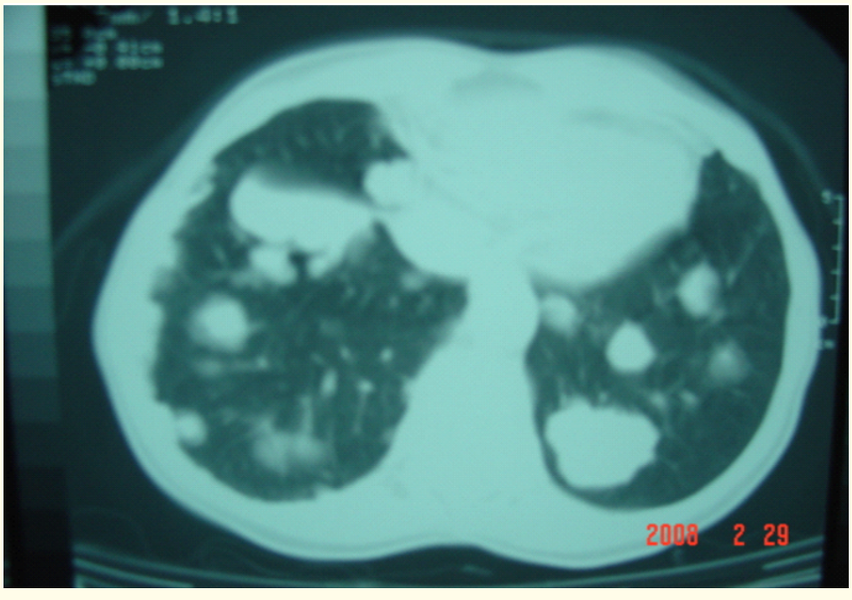

Figure 6: *Patients with a history of malignant melanoma with multiple bilateral pulmonary metastases.*

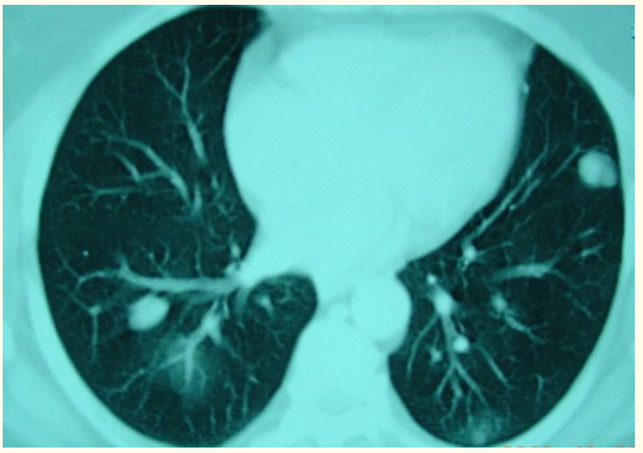

Figure 7: *CT chest showed bilateral pulmonary metastases (resectable).*

This examination allows a consistent anatomical very important with reference to intra thoracic structures and for planning resection and extent of surgery [14]. Other tests that can be part of the preoperative evaluation, include bronchoscopy, CT of the abdomen and pelvis, magnetic resonance imaging (MRI) and bone scintigraphy; in some cases it is important to get the levels of tumor markers such as CEA (colorectal tumors), α-fetoprotein and β-HCG (germ cell tumors).

More recently, positron emission tomography (PET-CT) with fluorine-18 deoxyglucose has been shown to be a new modality in the evaluation of patients with lung metastases, however, due to its high cost, your statement may be questionable. It is known that PET-scan has limited sensitivity in nodules < 1 cm, which is not higher with integrated PET-CT [15]. On the other hand, the higher value of PET-CT is its high sensitivity to detect extra thoracic recurrence, information that can alter the surgical plan. PET-CT can also better assess the extent of intra-thoracic disease, such as the presence of mediastinal lymph nodes (Figure 8). In this context, it is important to define the PET-CT negative for the lung node should not influence the conduct of state to surgical resection, provided that there is strong suspicion for this, especially in nodules growth during the follow-up [16].

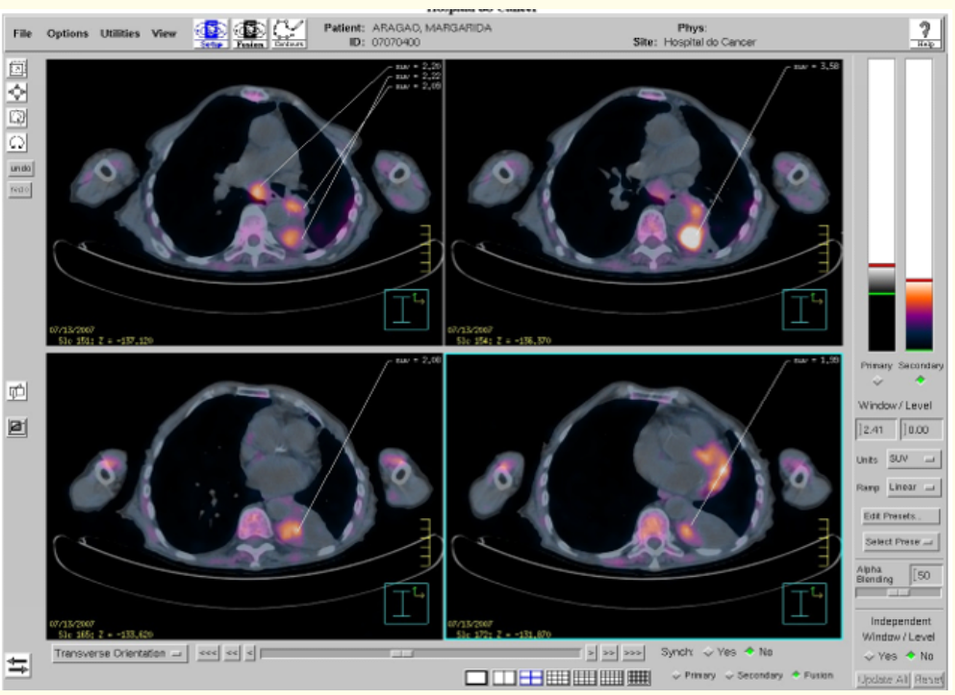

Figure 8: *PET-CT showing lung metastasis with LLL atelectasis and hilar and mediastinal lymph nodes.*

The PET-CT has a sensitivity of 50%, specificity of 98% and accuracy of 87% for lung metastasis, compared with helical CT of 75%, 100% and 94% respectively [16]. Most authors agree that both imaging modalities should be complementary in order to assess extent of disease and during follow-up.

Factors such as evaluation of the anatomic extent, characterization of solitary pulmonary nodule - in squamous cell carcinomas - and metastatic primary lung tumors, evaluation of extra thoracic disease and regional lymph nodes, should help as additional clinical information which is required for treatment planning [17].

Prognostic factors

Survival prognostic factors are related to patient characteristics (ex. age, sex, symptoms, diagnosis and location) or to tumor related characteristics itself, and its treatment (tumor size, neoadjuvant and adjuvant chemotherapy, disease-free interval) and factors related to lung recurrence (number of metastases, the laterality of nodes, number of thoracotomies, the last resection, histopathological aspects, molecular markers). The search for characteristics that allow to predict clinical behavior of certain disease is of great importance, especially for treatment planning. The following factors should be assessed individually in each patient according to the histological type in question:

- Sex;
- Age Group;
- Topography of the primary tumor;
- Neoadjuvant chemotherapy;
- Adjuvant chemotherapy;
- Disease-free interval;
- Laterality of pulmonary involvement;
- Number of nodes identified at chest CT scan;
- Number of metastatic nodules resected;
- Size of largest nodule resected;
- Number of thoracotomies;
- Type of pulmonary resection;
- Presence of hilar or mediastinal lymph node;
- Resectability of lung metastases - complete x incomplete;
- Association of chemotherapy to surgical treatment of metastases: neoadjuvant or adjuvant

Younes., *et al.* recently reported a retrospective study of 529 patients undergoing pulmonary metastasectomy of different histologies, that for those with disease-free interval (DFI) less than 12 months, there was a significant worsening of overall survival, but this factor did not show statistical difference in the multivariate analysis [18].

Pastorino., *et al*. analyzed 5206 cases of tumors of various histologies and showed that 31% of patients had 11 months DFI, 36% had 12 to 35 months and 31% with 36 months or more. Observed different survival rates, for patients with DFI < 11 months, survival was 33% in five years and a median of 29 months, for those with DFI between 12 and 35 months, survival was 31% in five years and a median of 30 months, those who had DFI > 36 months, survival was 45% in five years and a median of 49 months [4].

Although there is a consensus in the literature that the DFI is a prognostic factor, some authors disagree with such information. Although not confirmed in previous reports, probably, the research methods and interpretation are different in each report.

Some authors make their calculations for a fixed DFI, while others look for a DFI with the best statistical difference. The best results are obtained with disease-free interval > 12 months.

Pulmonary metastases can be accompanied by hilar or mediastinal lymphatic involvement, it is believed, though unproven, that the disease may spread to lymph nodes by lung. Retrospective series and autopsy revealed nodal metastatic disease, and 5% to 33% of cases, depending on the histological type. Thus, they are more common in carcinomas than in sarcomas. Although the presence of thoracic lymph node metastasis is a negative prognostic factor, systematic lymphadenectomy has no defined role [19-21].

Prognosis of patients with metastatic disease appears to be largely determined by the number of metastatic nodules, according to several authors [14-17]. However, a subgroup analysis of patients reported with multiple metastatic nodules treated with complete resection, noting that such an approach was a strong positive predictor of survival, reducing the impact of the high number of metastases on survival. Rusch., *et al.* reported that patients with pulmonary nodule solitary metastasis had better survival [2]. Younes., *et al.* showed in a prospective study of pulmonary metastasectomy in 529 patients with tumors of various histologies, the number of resected nodules greater than two unfavorable correlated with survival, a significant feature in the univariate ($p = 0.0007$) and multivariate ($p = 0.016$), both overall survival and disease-free survival ($p = 0.003$ and $p = 0.004$) in univariate and multivariate analysis, respectively [18].

Surgery is one of the most important variables influencing the prognosis of patients, although complete surgical resection of metastasis does not provide the recurrence of cancer [16]. Several authors have emphasized that patients undergoing pulmonary metastasectomy and complete resection cancer was a prognostic factor of greater impact, and associated with a longer survival. Patients treated with complete resection can present five-year survival between 30% and 40%, and patients with incomplete resection, a survival rate much lower, below 10% [2,22-24].

Surgical Technique

In selected patients, resectable lung metastases in the absence of extrapulmonary disease, complete resection is associated with increased overall survival. In selected patients even more, in which extra thoracic metastasis were operated (ex: liver), the indication of resection pulmonary aims to remove all disease at first detected. In these cases, the surgeon has in its favor the knowledge of tumor biology (ex: colorectal cancer), in which the dissemination is made to preferred organs (ex: lung and liver).

The decision between minimally invasive and conventional thoracotomy or sternotomy, depends on the number, location and size of metastasis. The main objective is to remove all node (s) with a gross margin of at least 1 cm. The open surgery or conventional, with more limited incisions in the skin, associated with muscle-sparing thoracotomy, have gradually replaced the classic posterolateral thoracotomy - with the intention to reduce the trauma to muscle function and pain after surgery - thereby promoting early mobilization of the patient.

Other authors recommend further staged axillary thoracotomy for bilateral metastases as an alternative to conventional thoracotomy [25]. There is considerable controversy about patients with unilateral disease diagnosed by chest CT, with respect to unilateral or bilateral approach. Since CT scans can miss up to 24% of multiple lesions, some patients are operated upon bilateral approach (sternotomy or thoracotomy). However, improvements in image quality by helical CT and positron emission tomography with FDG PET-CT in preoperative evaluation, increased the accuracy of staging and selection of patients for decision on unilateral or bilateral approach [16]. The video-assisted thoracic surgery (VATS) has been proposed as a procedure with less morbidity for lung metastasectomy. This approach has obvious appeal because of shorter hospital stay and less postoperative pain when compared to sternotomy or thoracotomy. The VATS often has been used as a diagnostic procedure - especially in cases with a single nodule - and as a curative potential in pulmonary metastasectomy, especially for lesions located in the outer third of the lung with up to three centimeters [10,11]. The deeper lesions, or smaller, cannot be detected by thoracoscopy. In addition, for patients with multiple metastases, palpation of the lesions during the stapling offers greater security with regard to the resection margins [9,25-27].

The possible incisions for resection of metastasis include thoracotomy, staged bilateral thoracotomy, sternotomy, bilateral thoracotomy (Clamshell incision) and minimally invasive (VATS). The incision of choice should not influence the survival of all patients, when the main goal is complete resection. There are advantages and disadvantages of each choice in access for bilateral lesions (Table 3).

Surgical technique	Advantages	Desadvantages
Postero lateral thoracotomy	Excellent exposure	Major pain; need for reoperation and more morbidity
Median sternotomy	Simultaneous bilateral exposure; less pain	Difficult access to the hilum, posterior segments and lower lobes
Anterior bilateral thoracotomy (Clamshell)	Excellent exposure, less pain than conventional thoracotomy	Possibility of internal mammary vessels lesion and possible difficult access to posterior segments or lobes
VATS	Good visualization; less pain and morbidity	No palpation; difficult access to deeper and central lesions

Table 3: *Characteristics of each surgical approach - advantages and disadvantages.*

Conclusion

The radical surgical resections of lung metastases in appropriately selected patients may offer increased disease-free survival without systemic treatment. Retrospective studies with large samples have shown that survival rates at five and 10 years can reach 35% and 25%, respectively.

Since completely resectable through assessment by helical CT of the chest, even for bilateral disease, the metastasectomy may be indicated, with interesting results of survival. Some histological types of lung metastases may play a role at reoperation with curative intent and survival. However, for some tumors with symptomatic metastasis, surgery may be indicated, even if the primary tumor is not completely controlled.

For patients with single pulmonary nodule, even in previously treated tumor, the possibility of primary cancer should be considered, specially in those patients with previous history of smoking, when the pulmonary lobectomy with lymph node dissection is the treatment of choice.

The long-term follow-up chest CT every 3 - 4 months is mandatory, and all nodes of recent onset must be regarded as new metastases.

The results published in the literature confirm that lung metastasectomy is a potentially curative treatment. The resecability, the disease-free interval, and the number of resected nodules, are the most important predictors of survival.

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