Review Article

Pulmonary metastasectomy: an overview

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Abstract: Metastasectomy is the most frequent surgical resection undertaken by thoracic surgeons, being the lung the second common site of metastases. The present oncological criteria for pulmonary metastasectomy are: (I) the primary cancer need to be controlled or controllable; (II) no extrathoracic metastasis—that is not controlled or controllable—exists; (III) all of the tumor must be resectable, with adequate pulmonary reserve; (IV) there are no alternative medical treatment options with lower morbidity. General favourable prognostic features in patients with pulmonary metastases are: (I) one or few metastases; (II) long disease free interval; (III) normal CEA levels in colorectal cancers. Negative predictive features in patients candidate to pulmonary metastasectomies are: (I) active primary cancer; (II) extrathoracic metastases; (III) inability to obtain surgical radicality; (IV) mediastinal lymphatic spread. The lack of controlled trials and studies limited by short follow-up and small cohorts did not allow to overcome some skepticism; moreover, the heterogeneity of these patients in terms of demographic, biologic and histologic characteristics represents a clear limit even in the largest series. On the basis of present knowledge, without results coming from on-going randomized trials, radical resection, histology, and disease free interval seem to be independent prognostic factors identifying a cohort of patients maximally benefitting from lung metastasectomy.

Keywords: Lung metastases; metastasectomy; pulmonary function

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Introduction

Metastasectomy is the most frequent surgical resection undertaken by thoracic surgeons (1). Lung is the second common site of metastases (1) and the role of pulmonary metastasectomy has been widely investigated by the 1970s (2) culminating in an important landmark publication in 1997 reporting the results from the International Registry of Lung Metastasectomy (3,4).

From 2000 through 2011 the performance of all types of metastasectomy—irrespective of the anatomic target site (liver, lung, brain and adrenal glands)—increased substantially across common cancer types, notwithstanding various advances in systemic therapies; metastasectomy was performed more safely, despite increasing patient comorbidities and lung metastasectomies increased significantly, following liver metastasectomies that demonstrated the highest rate of increase of any metastatic site (5).

Colorectal neoplasms are the commonest epithelial lesions for which pulmonary metastasectomy is indicated (1) and they are the only type of primary cancer metastatic to the lungs for which a randomized trial is ongoing, comparing active monitoring versus active monitoring with pulmonary metastasectomy (6).

All the other types of primary cancers metastatic to the lungs (germ cell tumors, melanoma, sarcoma, gyneacological, urological, upper gastrointestinal as well as thyroid and kidney cancers) have been studied only by

non-randomized studies and the evidence for pulmonary metastasectomy still remains unproven (1).

Oncologic principles and surgical aspects

The present oncological criteria for pulmonary metastasectomy are: (I) the primary cancer need to be controlled or controllable (II) no extrathoracic metastasis—that is not controlled or controllable—exists (III) all of the tumor must be resectable, with adequate pulmonary reserve (IV) there are no alternative medical treatment options with lower morbidity (7).

Patients with favourable prognostic factors can survive longer irrespective of treatments while favorable predictive factors are those allowing to discriminate patients benefitting from particular treatments (8); general favourable prognostic features in patients with pulmonary metastases are: (I) one or few metastases; (II) long disease free interval; (III) normal CEA levels in colorectal cancers. Negative predictive features in patients candidate to pulmonary metastasectomies are: (I) active primary cancer; (II) extrathoracic metastases; (III) inability to obtain surgical radicality; (IV) mediastinal lymphatic spread (1).

It is estimated that 75% or more of patients with pulmonary nodules will also have metastases to extrathoracic sites; only 15% to 25% of patients have lesions confined to the lung and are appropriate candidates for curative resection (7). For this reason, staging for metastatic disease outside of the lung is performed prior to pulmonary resection, by CT of the chest and abdomen and, in selected cases, by PET scan and brain imaging with either MRI or CT scan (9).

Intrathoracic lymph node involvement is associated with decreased survival after pulmonary metastasectomy; the data are most convincing for colorectal and renal cell cancers and there is limited evidence as to whether mediastinal lymphadenectomy leads to improved survival in patients receiving lung metastasectomy (10-12).

Lung function testing is an important component to the preoperative evaluation of patients undergoing metastasectomy: although sublobar resections are most often used, cumulative parenchymal loss must be considered in the setting of multiple lesions (7,13); moreover, although "parenchyma-sparing" procedures still remain the gold standard, major pulmonary resections for treating lung metastases—including pneumonectomy or pulmonary resection with en bloc resection of the chest wall or other major structures (diaphragm, pericardium, superior vena cava)—have been reported with low mortality and morbidity rates and an acceptable long-term survival, when performed in selected patients susceptible to complete resection (14).

Patients with a predicted postoperative FEV 1 or DLCO between 30% and 60% predicted should have additional risk stratification with an exercise test, such as shuttle walk test or stair climb, prior to proceeding with surgery; patients with postoperative predicted FEV 1 or DLCO less than 30% should undergo formal cardiopulmonary exercise testing with measurement of maximal oxygen consumption (15).

Both video-assisted thoracic surgical (VATS) techniques and open thoracotomy are accepted as appropriate incisions for performing pulmonary metastasectomy (16); on one side, open techniques have been shown to lead to the detection and hence, resection of more metastases than VATS techniques, in particular in case of nodule deeply embedded within the parenchyma (16-18). On the contrary VATS has been considered a preferable approach due to superior functional outcome, offering a shorter hospital stay, a shorter duration of chest tube drainage and epidural analgesia (19) (*Figures 1,2*).

Colorectal cancers

A quarter of patients with colorectal cancer have metastatic lesions at diagnosis and in nearly half of them, metastases will develop, often in liver or lung or both (20). Surgery has been consistently reported as a potentially curative option for liver-limited disease , with 5-year survival of 30–40% (21); in 10–15% of cases lung metastases are documented at advanced disease and are diagnosed mostly as multiple or bilateral metastases, with only 2% to 7% a single lesion (22).

The practice of pulmonary metastasectomy is widespread, having a consensus regarding the effectiveness of the procedure with 5-year survival rates approximately 30–50% (23); however, despite its widespread use, no results from prospective controlled or randomized trials are now available to confirm the evidence-based benefit of lung surgery (20).

Recently the GLIDA trial disclosed that early diagnosis of neoplasm recurrence is not related to overall survival implementation (24).

As reported before, the PulMiCC trial—comparing active monitoring versus active monitoring with pulmonary metastasectomy in patients suffering from pulmonary metastases from colorectal neoplasms—is ongoing and it will be probable able to provide evidence with respect to pulmonary metastasectomy in colorectal cancer (6,25).

Figure 1 Multiple, bilateral lung metastases not amenable of radical resection because of number, location and dimensions of the lesions.

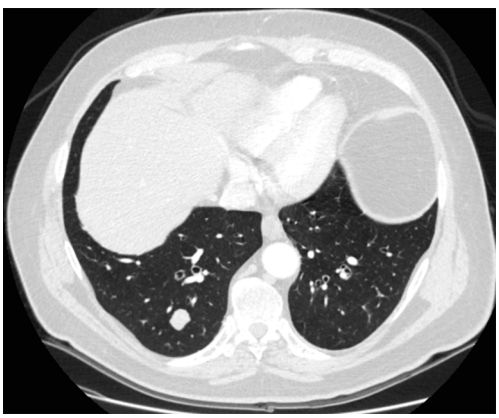

Figure 2 Single metastasis of the right lower lobe amenable of radical resection.

A recent study disclosed that major anatomic resection with lymphadenectomy for pulmonary metastasectomy can be considered in selected patient with sufficient functional reserve to improve the disease specific survival and disease free survival (26); nowadays is commonly stated that radicality of surgery is the major prognostic indicator of long-term survival, whereas number and distribution of lung metastases, primary stage at diagnosis, elevated prethoracotomy carcinoembryonic antigen levels, disease-free interval, mediastinal or hilar lymphnode involvement, presence of solitary liver localization and systemic therapy are otherwise considered in retrospective studies (20).

Urinary tract cancers

After the initial report, there have been anecdotal reports that suggested the potential benefit of metastasectomy on survival of patients with urinary tract cancer (26,27). However, due to the rarity of oligometastases associated with advanced urinary tract carcinoma, little is known about the efficacy of metastasectomy and prognostic factors (27).

Despite a favorable initial response rate to chemotherapy (44–64%), long-term overall survival is achieved by only a minority of patients with metastatic urinary tract cancer and the median overall survival for this disease typically plateaus at approximately 14 to 15 months (28). In studies investigating the contribution of lung metastasectomy in patients with metastatic urinary tract cancer, overall survival was 30 months, longer when compared with that of patients who received mainly systemic chemotherapy (27).

For patients with isolated pulmonary metastases, metastasectomy for single lung metastasis is statistically related to longer time to progression than for patients receiving multiple lung metastasectomies but a longer time to progression does not translate into a longer overall survival (27).

The present recommended strategy for consolidative surgery for metastatic tract cancer suggests to offer this treatment to patients who: (I) have responded to previous chemotherapy; (II) have disease recurrence at the initial or sole metastatic site; (III) have a tumor that is surgically resectable with clear margins; (IV) have a documented period of disease stability without evidence of rapid disease progression (29).

In case of renal cell carcinoma, patients receiving lung metastasectomy disclosed a significant survival advantage, mainly in case of isolated pulmonary metastases, although a survival advantage was observed even in patients with extrathoracic synchronous metastases receiving pulmonary resection (30); it is not clear if patients should receive lung metastasectomy when radical macroscopic radicality could not be achieved (30).

Osteosarcoma and soft tissue sarcomas

Sarcoma comprises a heterogeneous group of histologic subtypes with a propensity to metastasize to the lungs. Isolated pulmonary metastases occur in as many as 20% of patients diagnosed with soft tissue sarcoma and as many as

40% in those with a primary bone sarcoma (31).

Osteosarcoma is the most common primary cancer in young patients (32); three-fourths of patients metastases at diagnosis and about 30–40% of patients—without metastatic disease at diagnosis—develop subsequently lung metastases (33).

Lung metastasectomy provides prolonged survival and should always be considered when safely feasible (34); better outcomes are reported in patients with single-side metastatic disease and longer disease free interval (33); although the volume of lung lesion was not statistically related to postoperative prognosis, patients requiring a major resection—because of centrally located lesions—presented a poorer prognosis (35); post-chemotherapy necrosis <90% in the primary tumor, developing metastases during chemotherapy and chondroblastic subtype are predictors of poor prognosis (36).

Soft tissue sarcomas are an eterogeneous group of mesenchymal cancers (37); they frequently metastasize to the lung, despite primary tumor radical resection (38).

Pulmonary metastasectomy is considered the gold standard treatment in case of isolated lung metastases, as several studies have shown a better survival in patients who received metastasectomy (39,40).

According to Giuliano *et al.*, younger age at diagnosis and low-grade tumors with longer disease free interval offer the greatest survival advantage to radically resected patients (37).

Pediatric cancers

Primary solid cancers of children, such as Ewing's sarcoma, hepatoblastoma, Wilms' tumor and osteosarcomas, commonly metastasize to the lung, having a negative prognostic impact (41).

Several reports have shown prolonged survival after pulmonary metastasectomy in selected patients presenting with isolated lung metastases, mainly in case of osteosarcoma; however prognostic factors are still unclear (42,43). The 5-year survival rates—reported by studies on the role of surgery for pulmonary metastases in pediatric patients—ranged from 20% to 40% (44,45).

Tronc *et al.* reported that pulmonary metastasectomy is a safe and potentially curative treatment in pediatric patients presenting secondary lung lesions form solid tumors of different histologies.

The low morbidity rate—as well as the absence of mortality—justify an aggressive surgical approach combined with chemotherapy; ideal indications for lung metastasectomy are a small number of pulmonary metastases and a long disease free interval (41).

In a recent report from Stanelle *et al.*, the influence of pulmonary metastasectomy for metastatic synovial sarcoma in pediatric/adolescent patients has been investigated, disclosing that pulmonary metastasectomy may be associated with improved survival if complete resection is achieved (46).

Head and neck cancers

The lungs are the most common target of distant metastases form head and neck cancers, including squamous cell carcinoma, adenoid-cystic carcinoma and other histologies (47,48). These metastatic cancers scarcely respond to chemotherapy, and thus surgery has become a valid curative alternative if all the general principles of lung metastasectomy are respected.

Five-year survival after lung metastasectomy of head and neck cancers is reported to range between 50–60% (49); older age (≥60 years), short disease free interval (<26 months) and histology of squamous cell carcinoma have been reported to have an adverse impact on clinical outcome (47,50); similarly oral cancers, mediastinal lymph nodes spreading and pleural infiltration conditionate a worse prognosis (51).

Patients receiving pulmonary metastasectomy of adenoid cystic carcinoma—a slow growing tumor—present an estimated 5-year survival rate of 84% (52); on the other hand, 5-year survival rate of patients undergoing lung resection for squamous cell carcinoma ranges between 26.5% and 43.0% (53,54).

Lung metastases and primary squamous cell lung cancer are difficult to be histopathologically distinguished; differential diagnosis is mainly based on clinical aspects (site of lung lesion, tumor stage, disease free interval) while, so far, genetic analysis does not allow to discriminate between metastases of SCC of the head and neck and primary SCC lung cancer (51).

Gynecologic cancers

The incidence of pulmonary metastasis of gynecologic cancers ranges between 2.3–4.6% (55) being higher in patients suffering from sarcoma or choriocarcinoma than in patients affected by epithelial gynecologic cancers like cervical, endometrial or ovarian carcinomas (56).

At the moment, The Clinical Practice Guidelines in Oncology developed by the National Comprehensive Cancer Network (NCCN) suggest surgical resection for

removable regional uterine cancer metastasis (55). Several studies have shown a 5-year survival rate from 32.9% to 46.8% (57,58).

Lung metastasectomy—when is a low risk-procedure—has been shown to ameliorate the long term survival; moreover, pulmonary resection, for single lung metastasis might offer a better prognosis not only for patients with a long relapse free interval but also for patients with tumors resistant to chemotherapy or re-recurrent ones (56). Patients presenting more than three pulmonary lesions and with respiratory symptoms, related to lung metastases, could expect to have worse prognosis after lung metastases resection (55).

Other malignancies

Melanoma

The lungs are the most frequent site of visceral metastases from melanoma, comprising 15% to 35% of patients with metastatic melanoma (59). Several studies have shown improved survival after pulmonary metastasectomy, with median survival from 10 to 28 months and 5-year survival rates from 4% up to 14–35% (60,61). Positive prognostic factors include complete resection, disease-free interval greater than 1 year, fewer than three pulmonary nodules, absence of extrathoracic and lymph node metastasis, and response to chemotherapy/immunotherapy (62,63).

Gastric cancers

The role of lung metastasectomy in gastric cancer patients is still unclear (64). As many patients suffering from lung metastases form gastric cancers present synchronous carcinomatous lymphangitis or pleuritis, pulmonary metastasectomy has been rarely reported in this setting, thus only few data being available on short and long term outcomes (65,66).

Lung metastasectomy for gastric cancer pulmonary metastases has been only rarely reported, therefore we conclude that pulmonary resection of gastric metastases has no evident role in the routinely clinical management of metastatic gastric patients and it could be occasionally proposed only for highly selected patients (64).

Nonseminomatous germ cell tumors

Nonseminomatous germ cell tumors of testicular origin are the most frequent cancers among male patients younger than 30 (67); but lungs and the retroperitoneal space are commonly the starting site of metastatic spread (68).

Indications for lung metastasectomy in this cohort of patients are: (I) lack of response to chemotherapy; (II) only partial response and then recurrence while on chemotherapy; (III) recurrence after standard and second line treatments; (IV) to check if residual tumor is still present; and (V) to resect expanding benign teratomatous aspects of the tumor (69). Postoperative 30-day mortality rate is reported to range between 0.0 and 0.036 while 5-year survival rates range between 73% and 94% (68).

Breast cancers

The lung is a frequent metastatic site for recurrent breast cancer but the role of pulmonary resection is still under debate, in particular in the light of excellent results of non-surgical treatments, like hormono or chemotherapy.

Yhim *et al.* analyzed clinical outcomes of patients suffering from recurrent breast-cancer with less than four pulmonary metastases, treated with systemic treatment alone or lung resection and then systemic treatment, disclosing that pulmonary metastasectomy can be an effective therapeutic option for patients with few and small metastases, irrespective of poor-prognosis aspects (70). Similarly Planchard *et al.* demonstrated that pulmonary metastasectomy from breast carcinoma was associated with a significant 5-year survival rate of 45%, but were not able to discriminate whether this result was due to the surgical procedure itself or to the selection of patients (71); the authors emphasized that when resection is evaluated this cohort of patients, both the size of the largest metastasis and the disease free interval should be carefully considered (71).

Conclusions

Since the establishment of the International Registry of Lung Metastases in the 1990s (3), pulmonary metastasectomy has been an area of debate between surgeons and oncologists (72). However, the lack of controlled trials and studies limited by short follow-up and small cohorts did not allow to overcame some skepticism; moreover, the heterogeneity of these patients in terms of demographic, biologic and histologic characteristics represents a clear limit even in the largest series (73,74).

On the basis of present knowledge, without results coming from on-going randomized trials, radical resection,

histology, and disease free interval seem to be independent prognostic factors identifying a cohort of patients maximally benefitting from lung metastasectomy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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