Lung metastasectomy: an experience-based therapeutic option

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For decades lung metastasectomy has been an empiric approach to the treatment of patients with lung metastases from a variety of tumors. This approach represented the only potential curative treatment. Although this therapy was based on well-known selective surgical criteria, the lack of a better alternative management largely contributed to its diffusion.

The indications to surgical treatment of lung metastases are constantly evolving (1-3). The most recent progresses of chemotherapy have subtracted to surgery many patients, including those with breast cancer or osteogenic sarcoma (4). In other cases, such as germ cells tumors, the efficacy of chemotherapy downgraded surgery to the "adjuvant role" of removing the minimal residual disease (5). A similar evolution can be indicated for the treatment of lung metastases from colorectal and renal cancer (6). Also in these cases some indications for the surgical treatment has progressively changed and the efficacy of chemotherapy as well as targeted therapies, suggests approaches other than surgery. Indeed, in colorectal metastases, a patient with indolent disease and a solitary metastasis associated with normal carcinoembryonic antigen (CEA) levels (7) and no metastatic lymph node remains the ideal candidate to lung metastasectomy (2). In other conditions the surgical choice is achieved case by case. Similarly, renal metastases deserve an accurate preliminary evaluation (8).

A number of issues still remain to be defined: the need and importance of mediastinal nodal staging, the role of minimally invasive surgery, the integration of surgery with nonsurgical treatment, the value of reoperations, and the indications for alternative modality of treatment such as ablation, stereotactic, radiotherapy and other (9,10).

Along our wide experience we crossed through all these novel steps bringing up to date the indications to surgery according to the most recent innovations. We always aimed at the efficacy and safety for the treatment as well as at the lesser trauma and the better quality of life for the patient.

According to Fiorentino and Treasure (11), we think that surgery of the lung metastases is based on evidence of clinical data rather than on professional opinion alone. Nevertheless, at present, the decision to operate still comes from the clinical experience of the single surgeon and from the preference of the patient who often becomes more confident on surgical results after detailed information.

The surgery of lung metastases has attracted our interest for several decades and we have largely speculated into many different aspects of this intriguing topic (12-23). In occasion of a recent analysis finalized at the role of reoperation for lung metastases (24) we reviewed our long experience. Herein we outlined the major issues derived from this analysis.

Major issues

To date, mandatory requirements for lung metastasectomy still remain the control of the primary tumor, the resectability of all viable lung metastases and prediction of adequate postoperative respiratory function and quality of life as well.

Recently, some authors prefer to speak of "primary tumor controllable" (2,3), which means the potential "eradication" of the tumor by surgical treatment predictable at the time of diagnosis. This behavior entails the resection or radical cure of the primary tumor even after lung metastasectomy.

Better knowledge in post-operative function prediction has enhanced the indications of lung metastasectomy. Indeed these evaluations allowed to accomplish of more aggressive resection and extensive reoperations.

Adequate respiratory reserve can be predicted by the calculation of the postoperative forced expiratory volume

in 1 second. At the moment, other instrumental techniques may provide further and more accurate information such as vibration response imaging (25), quantitative computed tomography (CT) (26) and technetium-99m-labeled macroaggregate of albumin single photon emission CT (27).

Extended resections

Classically the surgical removal of lung metastases entailed a limited resection of peripherally located lesions with the minimum possible loss of pulmonary parenchyma. Therefore centrally positioned metastasis requiring lobar or larger resections had been considered for a long time as non-ideal for lung metastasectomy. Nowadays major resection is not considered an absolute contraindication to metastasectomy when performed in selected patients susceptible to complete resection (28). Extensive and combined resections can be performed with low mortality and morbidity rates and an acceptable long-term survival (29). Our experience entailed combined one-stage multi lung-liver resections (19). In these patients we documented a satisfactory long-term survival in selected patients. Presence of simultaneous lung and liver metastases should not be considered an absolute exclusion criterion for metastasectomy. Because of the poor results observed, aggressive surgical strategies should be carefully reconsidered in the presence of high levels of CEA plus CA19-9 at first metastasectomy. So far we reached a total of 58 operated patients with simultaneous (n=24) and sequential pulmonary and hepatic (lung-liver: n=16; liver-lung: n=18) metastases (unpublished data).

Open vs. non-open surgery

The advancements in aesthetical and surgical techniques favored the safety of surgery and progressively extended the indications. In particular, the introduction of video-assisted thoracoscopy (VATS) has opened new frontiers that affected also the surgery of lung metastases.

The dogmatic statement of the superiority of manual bidigital palpation in detecting lung lesions compared to any other diagnostic device has strongly conditioned and limited the diffusion of non-open surgery in this setting (30). Therefore, surgery of lung metastases has been advocated for decades as ideal surgery for open accesses. Nevertheless, the significant clinical advantages of non-open accesses and the elevate diagnostic yield provided by the newest instrumentations have recently re-addressed the interest of the surgeon towards the non-open accesses. Migliore *et al*. found in a recent systematic review that the oncological results of VATS in terms of local recurrence and overall survival are equivalent to those achieved with open accesses (31). A large best evidence topic by Greenwood and West conducted in more than 153 papers confirmed that no differences were found in outcome between open and non-open accesses (32).

Transxiphoid hand-assisted metastasectomy

To allow bilateral manual palpation during VATS metastasectomy, in 1997 we developed a transxiphoid approach without sternotomy (15). This approach allowed an optimal manual palpation of the lungs (33). In our hands it allowed routine palpation of both lungs and easy one-stage bilateral VATS metastasectomy especially in the case of technically difficult nodules (18). We also demonstrated that this approach allowed better evaluation than helical CT in detection of pulmonary metastases (16). In a more recent paper based on a total of 219 lesions removed we reported a 19.3% of unexpected lung metastases and lesions sized less than 7 mm showed the highest false negative rate (22). With this approach we have recently passed the 300 resections for lung metastases. This procedure resulted less painful and less traumatic than any other thoracotomy. Respiratory function and most of the Short Form-36 domains recovered within 3 months from the operation (21). This approach was found valid for uniportal procedures for primary lung neoplasms and thymectomy (34) and we started a program for its wider employ.

Awake metastasectomy

The program "Awake thoracic surgery" was established and supervised by one of us (T.C.M), and was approved by the Research Ethics Board of our Institution in 2001. Subsequently, we re-named it "nonintubated thoracic surgery". It is the unique existing program at the Tor Vergata University and involves a dedicated group of surgeons, anesthesiologists, pulmonologists, physiologists, and physiotherapists. Over the years it generated a number of publications about different thoracic pathologies (35,36). The mastery acquired in this surgical technique allowed us to include the resection of peripheral metastases as part of the program (20). We adopted this technique in patients with radiologic evidence of peripheral solitary lung metastases. The procedure was performed under sole thoracic epidural anesthesia at T4 to T5 and to

reproduce bimanual-like full lung palpation, a modified digital-instrumental palpation method was employed. We experienced that the awake patients presented significant lower median operative time (25.5 *vs*. 48.5 minutes, P<0.00001), and hospital stay (2.5 *vs*. 4.0 days, P<0.02) with similar oncological long-term results to those achieved under general anesthesia. The experience with nonintubated surgery has progressively enlarged to a total number of 36 patients (unpublished data) and it has recently been object in a bad manner of a scientific evaluation by our previous coworkers.

Repeated metastasectomy

Recently, we have investigated the role and results of multi-reoperations for lung metastases performed with curative intent in 113 patients who underwent from two up to six lung metastasectomies (24). We proved that repeated metastasectomy did not imply a significant increment of perioperative mortality or morbidity. Initial recurrences tended to remain within the lungs thus redo metastasectomy had a rationale. Interestingly, we found that 5-year survival was significantly higher than the value recorded for patients undergoing only one metastasectomy and this was an artifact due to a multifactorial confounding effect dubbed survivability (37). We also experienced that tumors initially showed a less aggressive biological pattern and then became progressively more malignant and resistant to nonsurgical therapy (24). Similarly, size, number of resections and probability of recurrence increased by number of operation whereas disease free interval reduced. We think that redo metastasectomy was worthwhile for the initial procedures, afterwards both disease-free and overall survivals decreased and surgical therapy lost its efficacy.

Laser resection

In 1998 we published a prospective randomized trial to compare the usefulness of the neodymium: yttrium-aluminum-garnet (Nd:YAG) laser in resection of lung metastases (14). The trial involved 23 patients randomly treated with an Nd:YAG laser and 22 patients with a traditional diathermic device. The use of Nd:YAG laser was not associated with a significantly longer survival (log rank test, P=0.49). Laser resection allowed more tissue sparing (mean ratio lesion diameter/volume resected, 0.94 *vs*. 1.11, P<0.008). Univariate and multivariate analyses revealed the importance of laser use in reducing the number of days of postoperative air leakage (3.91 *vs*. 5.00 days) and hospital stay (7.50 *vs*. 9.90 days). Laser use significantly reduced tissue loss, postoperative air leakage, and hospital stay. Influence on long-term survival was not statistically proven.

In a subsequent 2001 paper we assessed the impact on survival of three types of resection: minimal by laser or conventional device and lobectomy in 85 patients (17). Again, the type of resection did not disclose statistically significant differences on survival, but laser patients showed shorter periods of air leakage and hospital stay.

Systemic inflammation

The role of inflammatory status in the host has recently become a major field of investigation in neoplastic setting and namely in metastatic process. In 2014 we have published a retrospective investigation based on prognostic value of preoperative inflammatory status markers from 44 patients who received curative-intent lung resection for colorectal metastases (23). Despite the modified Glasgow prognostic score (i.e., serum C-reactive protein and albumin levels) equal to 2 was a significant predictor of shorter progression free survival, systemic inflammation scores did not perform well as independent survival prognosticators.

Lymph nodes

The presence of metastatic lymph nodes is unanimously considered a strong predictor of poor survival after lung metastasectomy especially in those cases requiring anatomical resections (38). The lymph node ratio defined as the number of involved lymph nodes divided by the number of nodes examined has been recently advocated as potential prognostic factor for colorectal metastatic disease (39). On the other hand, the location of the involved nodes (mediastinal *vs*. hilar) does not seem to have a further negative effect on the prognosis (40).

Routine lymphadenectomy during resection of lung metastases reveals unexpected nodal involvement in a relevant proportion of patients, in particular in breast and renal metastatic disease (41). Although the suspect of metastatic lymph nodes should not represent per se a reason to avoid lung metastasectomy, routine lymphadenectomy may become an important prognostic tool and might influence further therapeutic decisions. In our experience we always perform video-mediastinoscopy of CT-PET positive nodes prior to surgical resection of lung metastases. However, lymph nodes are routinely resected during both

first and repeated metastasectomy even in the absence of imaging involvement. To date we found the 13% of apparently negative nodes are site of metastases and this percentage may redouble in the case of breast and renal cancers (unpublished data).

Prognostic factors

Classic clinical prognostic factors in the surgery of lung metastases aimed at predicting the evolution of the disease. Therefore they consist on tumor doubling time, disease-free interval, number and size of the lesions and production of humoral markers (1-3). All these factors provide information about the aggressiveness of the neoplasm and are indirectly related to the biological and genetic features of the metastatic cells. The probability of eradicating the disease often depends on these intrinsic properties, whose clinical prognostic factors represent only epiphenomena or, at least, consequences.

According to these considerations the clinical prognostic factors are progressively becoming less important, whereas biological and genetic features are assuming an increasing role as prognosticator and indicators for best-responders to surgery (42).

Conclusions

At present, surgery of lung metastases still has a precise role within an organic therapeutic plan, which should integrate all other non-surgical treatments. We always evaluate the opportunity for lung metastasectomy case-by-case according to several local factors, medical parameters and prognostic indicators.

Although there is no definitive scientific evidence about the effect of lung metastasectomy on long-term survival, several reasons collected during our long experience induce us to persevere with this therapeutic option. First of all, lung is the first and unique site of distant metastases for many neoplasms and for a long period. Second, lung metastasectomy is a safe operation which can be carried out with a constantly reduced morbidity. Third, the diagnostic device is providing, and will even better provide, an exact map of all resectable lesions. Final point, the development of genetic knowledge about the tumor cell suggest us to consider the metastasis as different case by case, thus outlining a subgroup of slow-growing lesions and therefore of best responder of patients. The challenge for the next future will be the individuation of this subset of subjects.

These new acquaintances will hopefully switch the concept of lung metastasectomy from an experience-based therapeutic option to solid evidence built on scientific bases.

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Footnote

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

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