

# Looking forward lung metastasectomy – do we need a staging system for lung metastases?

Marcello Migliore<sup>1</sup>, Michel Gonzalez<sup>2</sup>

<sup>1</sup>Section of Thoracic Surgery, Department of Surgery and Medical Specialities, University of Catania, Policlinico Hospital, Catania, Italy; <sup>2</sup>Section of Thoracic Surgery, Centre Hospitalier Universitaire Vaudois-1011, Lausanne, Switzerland

Correspondence to: Marcello Migliore, MD, PhD, FEBTS. Section of Thoracic Surgery, Department of Surgery and Medical Specialities, University of Catania, Policlinico Hospital, Via S. sofia 78, 95125 Catania, Italy. Email: mmiglior@unict.it.

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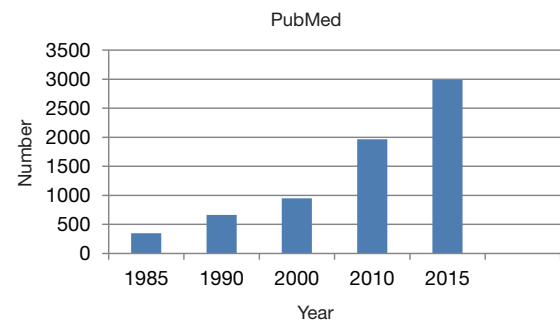
In the last decennium we are witnessing an impressive increase number of publications on lung metastasectomy (LM) ranging from commentaries, case series, comparative studies, reviews and systematic reviews as demonstrated in *Figure 1*.

The most common denominator between surgical papers is the tentative to demonstrate that LM may offer a prolonged survival. Moreover, the in deep review of the extensive literature demonstrated that the level of evidence to perform LM is weak and still today surgeons operated on the basis of their own experience (1-3).

The uncertainty on LM are several, and many questions remain unresolved. For example, the progression of metastasis is still not well known but it seems that it is mainly due to a small fraction of tumor cells with the capability to navigate from primary tumor cell to end-organ metastasis. For this reason it is possible that in the future the “so called” liquid biopsy to discover circulating tumour DNA (ctDNA) could detect the presence of ctDNA in the blood of patients with LM burden (4).

Unfortunately, most patients with pulmonary metastases will not be candidates for LM because the presence of comorbidities or the need of extended surgery (5,6). In these patients new approaches are available such as radiotherapy, radiofrequency and microwave ablation, and immunotherapy, but these treatments are in search of evidence (7). Recently, new strategies have been reported to obtain long term survival such as VATS lung suffusion, and a phase I trial isolating cisplatin for 30 minutes to the side of metastasectomy or primary lung cancer with oligometastases is underway (8).

As regards surgery, the indication for surgery in LM,



**Figure 1** Increase number of publications on lung metastasis.

oligometastatic or not, has a deep impact in the patient mood because the patients think that it is possible to eradicate the disease, and therefore to live longer (9,10). A recent survey in Spain demonstrated the presence of oligometastatic disease in 55% of patients (11). But some patients with a “resectable” metastatic disease in the lung will not survive longer as expected, and therefore the final results is that the practical operation to remove “resectable” disease is not the right operation which should have been performed. The obvious question is if it is ethical to operate a patient with “resectable” disease informing her/him that we have no prove that survival will be longer compared to the “no” operation group (12). In general, patients with lung metastases should be fit enough to undergo surgery, the primary disease site and any extrathoracic disease should be both controlled; complete resection of pulmonary involvement should be achievable with adequate pulmonary reserve; and no effective medical therapies should exist (13). Regarding the type of surgery, several techniques have been

**Table 1** Attempt of classification for lung metastases

Category	Description
T category	Primary tumor
T0	No evidence of activity
T1	Active
N category	Nodes
NX	Unable to assess
N0	No lymph node
N1	Intrathoracic node involvement
N2	Omolateral mediastinal or subcarinal node involvement
N3	Controlateral mediastinal node involvement
M category	Number of lung metastasis
M1	1 lung metastasis
M2 (b)	>1 but $\leq$ 3 lung metastases
M3 (b)	>3 lung metastases

For example, a patient with the main cancer in the colon or stomach or liver (or in another district) develops lung metastases, and has the following stage: T0N2M3 (b). T0 = the main tumor is under control; N2 has omolateral mediastinal nodal involvement; M3 (b)—more than 3 metastases in both lungs. The (b) means bilateral lung metastases, and the absence of e before TNM means “late appearance”.

proposed to perform unilateral or bilateral LM removing one or multiple metastases. Moreover few studies have demonstrated that no difference in survival exists between open surgery and VATS when LM needs to be removed (14–16). For this reason it is wise to conclude that the less invasive approach should be used, until proved differently. Furthermore another review reported that prolonged long term survival in LM of colorectal cancer is obtainable only in patients with single metastasis (17). Although some authors first reported that repeated metastasectomy could prolong survival, successively reviewing again the data they think that better survival attributed to LM may be due to the selection of patients who are innately destined to live longer (18,19).

During surgery, a positive node N1 or N2 adversely affects survival in LM, and the incidence of nodal metastases has an estimate of 20% to 25% across multiple tumor types (8). Although there is no definitive answer, we could speculate that nodal dissection should be performed mainly to stage accurately the disease than to prolong

survival. In another hand, pre-operative suspicion of lymph node involvement should also be investigated actively by mediastinal procedures (EBUS, mediastinoscopy, VATS) to confirm histologically the invasion to avoid unnecessary surgery (20).

The presence or absence of nodal metastases in LM is therefore an important point, and stimulates a question. Do we need a staging system for lung metastases? A staging system which focuses on lung metastases with the main AIM to categorize our patients, and predict survival is probably necessary. An attempt of staging system for lung metastases is shown and explained in *Table 1*. Time to metastasis (TM), defined as the time of appearance of lung metastasis, could also be added in the staging system to separate early from late lung metastases with an e (early) before the TNM, so that eTNM means an early appearance of lung metastases.

Finally, although the action of metastasectomy could be criticized as it could be seen as an overtreatment, on the other side it is difficult to explain to our patients that surgical resection of LM to prolong survival is in doubt. Should we deny this “hope” to our patients? Certainly not, we agree with some authors (3) that surgery is the current available hope that our patients have, and although there is the increase feeling of unfounded believe of longer survival with LM, we need to offer them the best treatment available.

Surgical opinion based on our own experience, but not on data, should not be the right approach anymore, and for this reason few years ago we joined the PulMiCC trial international (21). The PulMiCC trial, a vision of Tom Treasure, was initiated in UK in 2010 (22), after few years some European centers in Serbia and Italy joined the trial (23,24), which is now also open in China. Nowadays, technology permits a worldwide cooperation which will permit to collect data faster, and consequently large randomized controlled studies could be finish. The PulMiCC trial is representing an innovative worldwide scientific group with specific interest in LM to definitively answer if metastasectomy should be performed in patients with lung metastasis of colorectal cancer.

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M Migliore had the idea, designed and wrote the first draft of the manuscript; M Gonzalez agreed and contributed in writing. M Migliore and M Gonzalez approved the final version of the manuscript.

## Footnote

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

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