



TNM classification for lung metastases

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Abstract: Although extensively discussed in the field of oncology, lung metastases (LM) remains an important clinical dilemma full of uncertainty with many unresolved questions. The extensive literature shows that the level of evidence to perform LM is weak, and surgeons continue to operate on the basis of their own experience without formal guidelines. Furthermore, the recent results of the Pulmonary Metastasectomy colorectal (PulMiCC) trial showed no statistical differences on survival between operated and no-operated patients with lung metastases. It is obvious that we are caught in a dead-end, as it seems impossible to know whether or not surgery is indicated in pulmonary metastases or when other treatments should be preferred. The aim of this paper is to highlight the rationale, the possible advantages and future direction of the TNM classification for lung metastases. For these reasons, we re-propose a TNM classification for lung metastases which was published initially in 2016. The originally idea of the TNM classification of LM was born to explain how the number of metastases and nodal involvement interfere between each other to influence survival. We anticipate that in the amended classification the T will describe the number of metastases. We will also include the acronymous LM before the TNM (lmTNM) to differentiate it from the classical TNM classification for cancers. Time to metastasis (TM), defined as the time of appearance of lung metastasis, which is an important prognostic factor could also be added in the staging system to separate synchronous from metachronous lung metastases. Conclusion: We believe that the TNM classification for LM will simplify the indication for surgery and allow physicians, oncologist and surgeons to speak the “same language” in comparing their data and assessing the results of treatment of lung metastases.

Keywords: Lung metastases; TNM; classification; tumour

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Introduction

Although extensively discussed in the field of oncology, lung metastasis remains an important clinical dilemma full of uncertainty with many unresolved questions. Irrespective of the surgical approach, the most important aim of lung metastasectomy (LM) is to prolong survival. The extensive literature shows that the level of evidence to perform LM is weak since the uncertainty of the surgical results is real, and surgeons continue to operate on the basis of their own experience without formal guidelines.

Moreover, the choice between the available approaches such as radiotherapy, radiofrequency and microwave ablation, and immunotherapy is also debatable, as is the relative relevance of these treatments for each individual case.

To complicate things further, the recent results of the PulMiCC trial (1), which was an innovative trial with the goal to clearly answer if metastasectomy should be performed in patients with lung metastasis of colorectal cancer, showed no statistical differences on survival rate between operated and no-operated patients with lung metastases.

It is obvious that we are caught in a dead-end, as it seems impossible to know whether or not surgery is indicated in pulmonary metastases or when other treatments are indicated.

For all these reasons, we propose a TNM classification for lung metastases, which was published for the first time in 2016 (2).

This paper highlights the rationale, the possible advantages and future direction of the TNM classification for lung metastases.

Brief history of the TNM staging

The practice of dividing cancer patients into groups is more than 70 years old. The TNM staging system was introduced by Pierre Denoix, and successively developed by Clifton Mountain (3,4). Successively, the UICC created a committee for the classification of lung cancer based on TNM and the first edition was published in 1968. In 1973 Clifton Mountain, from the Anderson Cancer Institute of Houston in Texas (4) published the first 2,155 patients demonstrating that the principle of TNM staging system was correct and since then, nine editions of the TNM staging system of cancers have been reported (5).

The rationale of the TNM staging for lung metastases was developed from uncertainty

Following the 2010 ESTS project on lung metastases (6) and the 2nd Mediterranean Congress in Oncologic Thoracic Surgery, which was dedicated to lung metastases (7), very little changed in the surgical treatment and long-term survival of patients undergoing lung metastasectomy.

The indication for surgery in LM, oligometastatic or not, has a deep impact on the patient mood because it makes it (seemingly) possible to eradicate the disease, and therefore to live longer. Some patients with a “resectable” metastatic disease in the lung will not survive longer as expected, and therefore the final result is that the operation to remove “resectable” disease is not the right operation which should have been performed. It is noteworthy that the central question is whether or not it is ethical to operate a patient with “resectable” disease without proof that survival will be longer compared to the “no operation” group (8). This has been the driving force of the prospective randomized PulMiCC trial (9). The absence of clear longer-term survival of surgery patients *vs.* no-surgery patients acutely poses the never-ending dilemma: operate or not? In

addition, the updated analysis of 93 randomized patients of the PulMiCC trial, which suggests that the “no surgery” (control) patients survival is much better than previously assumed (1) increases the level of uncertainty on what is the right decision to take. Nevertheless, in the absence of clear-cut data, we are still in favor of lung metastasectomy as hope should not be denied to these patients, and “hope” might even stimulate a patient’s positive response to cancer. A recent study theorizes in fact that an individual’s level of hope is often determined by native personality and environmental factors, the authors argue that hope can be a therapeutic objective and review evidence showing the effects of hope-enhancing therapies (10). The additional problem is that pulmonary metastatic disease cannot be considered a single entity but rather is a heterogeneous disease with varying clinical presentations (synchronous/metachronous, single/multiple metastases, uni/bilateral) reflecting the biological aggressiveness of the disease.

A staging system for lung metastases was proposed in 1998 by Pastorino, McCormack and Ginsberg but the foundation for the staging system were profoundly different from the TNM classification, which we designed in our previous paper (11).

It was not the number of metastases which stimulated the idea of the TNM classification of LM but it was the presence or absence of nodal metastases in LM, and how the number of metastases and nodal involvement interfere between each other to influence survival (*Table 1*). The reason is explained by the evidence that positive node N1 or N2 adversely affects survival in LM patients, and the incidence of nodal metastases has an estimate of 20% to 25% across multiple tumor types (12). Nodal dissection should therefore be extensively investigated with EBUS, mediastinoscopy to confirm the involvement avoiding unnecessary surgery.

Proposed TNM classification for lung metastases

Our previous proposal for TNM included only number of pulmonary metastases, involvement of lymph node and active disease (*Table 1*). With current knowledge of pulmonary metastases, many important aspects have been missed like the laterality of the disease (uni-/bilateral), the moment of appearance (metachronous/synchronous) or the presence of other sites for metastases. All these elements should be integrated in the next TNM classification for lung metastatic disease.

The aims of TNM classification of Lung Metastasis do

Table 1 First reported TNM classification for lung metastases. Modified from Figure 1 of *Ann Transl Med* 2016;4:6. doi: 10.21037/atm.2016.03.15

| Category | Description |
|------------|---|
| T category | Activity of Primary tumor |
| T0 | No evidence of activity |
| T1 | Active primary tumour |
| 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 ≤3 lung metastases |
| M3 (b) | >3 lung metastases |

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: T0N2M2 (b). T0 = the main tumor is under control; N2 has mediastinal nodal involvement; M2 (b) 2 metastases in both lungs. The (b) means bilateral lung metastases, and the absence of e before TNM means "late appearance". As we wrote in the text the T and the M will be modified in the next amended TNM version.

not differ from those already known.

- ❖ Aid in planning of treatment;
- ❖ Indication of prognosis;
- ❖ Evaluation of the results of treatment;
- ❖ Exchange informations between centers;
- ❖ Minimize uncertainty.

An update of the previous proposed TNM dedicated to lung metastases would serve that purpose well and could even spark similar steps for other organs involvement. Although our previous TNM classification system is based on the assessment of only three components (2), the evolution of the first TNM classification for lung metastases should be based on the assessment of similar components but with the addition of numbers to these components indicate the extent of the disease and bilaterality. As a general rule all factors should be confirmed microscopically.

Our first paper on TNM classification of lung metastases (2) did not unfortunately reach the wide audience that we had

expected. After a few more years of reflection, we still think that the dedicated TNM classification could change the way of seeing and treating lung metastases, and therefore some amendments should be included to make the classification more understandable. These will be reported soon. We anticipate that in the amended classification the T will describe the number of metastases. We will also include the acronymous lm (lung metastases) before the TNM (lmTNM) to differentiate it from the classical TNM classification for cancers. Time to metastasis (TM), defined as the time of appearance of lung metastasis, which is an important prognostic factor could also be added in the staging system to separate synchronous from metachronous lung metastases.

The future of the TNM classification for lung metastases

Certainly, our project on TNM classification for lung metastases needs to be openly elaborated and validated. We envisage in the near future further discussion within major Societies and Organizations. A steering committee probably will be necessary to pursue studies to validate the appropriateness of the TNM staging for lung metastases, and probably for other organs liver, brain.

The recommendations for the use of clinical stage classification of lung metastasis should be therefore accepted by many Societies and Organizations. A meeting should be organized to acknowledge the need for the lmTNM classification so that data can be accumulated over a reasonable period of time. Our feeling is that major intellectual and scientific input are welcome and necessary to review the current and future version of the classification.

Without doubt, such a classification will allow physicians, oncologist and surgeons to speak the "same language" in comparing their data and assessing the results of treatment of lung metastases, a disease with highly heterogenous clinical presentations. Moreover indication for surgery in LM will be facilitated and personalized (13,14).

Our ongoing studies, to be published later, preliminarily indicate that the proposed scheme for describing the TNM staging of lung metastasis will be easily applicable to every patient with cancer who develops lung metastases.

In conclusion, the new TNM classification for lung metastases include many clinical aspects of metastatic disease with the main intention to unify and update existing views and experiences, to make indication for surgery homogeneous internationally, to facilitate data for prognosis

and to make research easier.

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