Perspective

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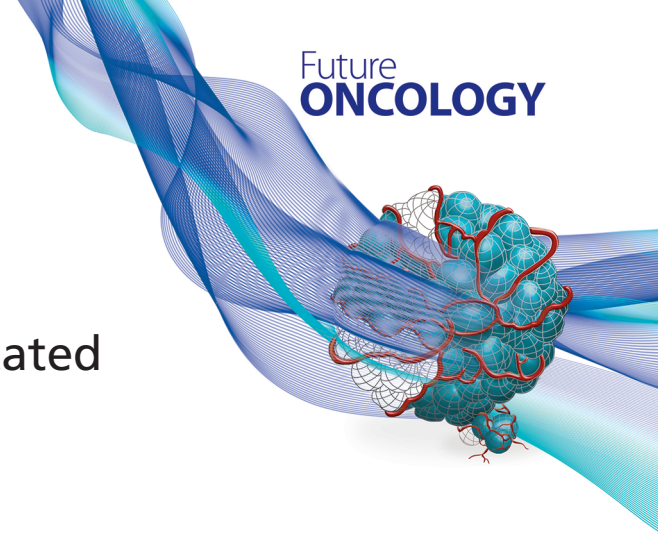

The second modification of a dedicated staging system for lung metastases

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The topic of pulmonary metastases has long been of high interest and ongoing controversy. There is a group of patients with pulmonary metastases who may benefit from curative resection. It remains unclear which among them will benefit from surgery in terms of survival. This work updates a previously proposed classification system for pulmonary metastases, similar in its essence to the tumor, nodes, metastasis (TNM) classification used for primary tumors and named pmTNM classification, where 'pm' stands for 'pulmonary metastasis'. The objective is to allow future studies to explore predictive and survival prognostic factors for pulmonary metastases and separate patients who will benefit from lung metastasectomy from those who will not. The secondary aim is to provide a classification system that will allow physicians, oncologists and surgeons to speak the same language in comparing their data and assessing the results of treatment of lung metastases.

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The surgical management of pulmonary metastases (PMs), namely lung metastasectomy (LM), has long been a topic of high interest and ongoing controversy along a number of fault lines (surgery vs nonsurgical; curative vs palliative management). Patients with pulmonary metastases represent a considerable number of cases since cancer is common. This makes them an important oncological challenge. However, there is a group of patients with PMs who may potentially benefit from curative resections [1], although no clear definition of this group exists. Many practitioners apply their own criteria to select those patients whom they think will benefit from one type of management, but, overall, there is a clear lack of agreed-upon selection criteria.

The concept of an oligometastatic state was proposed in 1995 and defined as an "*intermediate state between purely localized lesions and those widely metastatic amenable to a curative therapeutic strategy*" and is generally considered "*amenable to localized therapy*" [2]. Although the definition of an oligometastatic state is relatively vague in terms of the number of metastatic sites and lesions suitable for local treatment, Hellmann and Weichselbaum's landmark paper introduced the idea that patients with limited numbers of metastases previously thought to be incurable might be cured with local cancer treatments, including surgical resection. As many selected patients with PM have experienced prolonged survival or even cure, LM is currently practiced among all thoracic surgical centers and represents between 10 and 15% of their surgical activities [3,4].

Most surgeons today rely mainly on their experience and on a multidisciplinary discussion to assess the suitability of LM for a given patient with PM. In most centers, the decision-making process is articulated as follows: patients eligible for curative surgical resection of PMs should meet at least five specific criteria: the primary tumor is controlled; complete resection of all pulmonary lesions is possible; extrathoracic simultaneous liver lesion should be removed; the patient will tolerate surgical resection and, finally, indications must be decided after the interdisciplinary multimodal meeting discussion [5,6]. This group of patients is suitable for localized surgical

treatment, and most tolerate the surgery without major complications. This decision-making algorithm does not, however, identify which patients in this group will benefit from surgery in terms of prolonged survival, a question that is of course critical for the care process of patients with PM. It would be useful to refine these criteria to help identify them before surgery.

Numerous retrospective studies on LM have identified prognostic factors of extended survival: complete resection; single metastasis; long disease-free interval; type of primary tumor and absence of thoracic mediastinal/hilar lymph nodes involvement [7–10]. While there does not seem to be any single unequivocal criterion by which to make the best possible surgical decision, these studies suggest that pulmonary metastatic disease has very diverse clinical presentations (single/multiple/bilateral metastases, synchronous/metachronous, hilar/mediastinal lymph node involvement, previous extrathoracic metastases) correlating with the biological aggressiveness of the metastatic disease. This also demonstrates the great heterogeneity of pulmonary metastatic disease.

Recently, the PulMiCC trial has questioned the role of LM, reporting no statistical differences in survival rate in a randomized controlled trial with 93 patients. This study compared pulmonary metastasectomy patients with a nonsurgical group and reported a median survival after metastasectomy of 3.5 years (95% CI: 3.1–6.6) compared with 3.8 (95% CI: 3.1–4.6) years for the control group [11]. Because of poor recruitment, the study was stopped and the small number of participants in the trial precluded a conclusive answer to the research question, although it did shed light on the very best survival rates that can be achieved without surgery. Unfortunately, the study does not allow us to conclusively dismiss surgery since it included patients with different clinical presentations.

Part of the difficulty in disentangling these aspects is that PMs should not be considered a single entity, but rather a heterogeneous disease where clinical presentations may be correlated with the biological aggressiveness of the metastatic disease. In addition to clinical aspects, several biomarkers are currently being investigated to help physicians decide whether or not a surgical approach is useful [5]. The sheer diversity of biological and histopathological realities encompassed by the PM diagnosis might have blinded many healthcare providers to the fine-tuning it requires. Such elements include the progression mechanisms of PMs and their recurrence patterns, the correlation and timing between a PM and other metastases or comorbidities, or the lack of evidence for any treatment because there is simply no way to design a suitable control group. Finally, it should be noted that most patients facing a diagnosis of PM will want to attempt every possible treatment to make sure that the disease is eradicated and their life is prolonged, even if their perception on both points might be misguided. Although it does seem to correspond to the reality that there is no single best criterion to make a fully informed decision on PM, because it is a complex disease, it is abundantly clear that some patients will benefit from LM and may even fully recover from their disease and enjoy extended survival.

In this paper, we build on these reflections and on the obvious fact that each PM should be assessed individually. Yet, instead of refining selection criteria, we approach this question by adding more nuance to the disease description and by reflecting clinical aspects in the way PMs are classified. We intend to base this proposal on clinical evidence from relevant scientific research and define classification categories that add clarity to the decision-making process after the complete resection of the primary tumor. We modify our previous classification system for PMs, similar in its essence to the TNM classification used for primary tumors. The aims of this updated classification do not differ from those already known: planning of treatment; prognosis; evaluation of the results of treatment; information exchange between centers; and minimization of uncertainty. Moreover, the classification may allow a more precise treatment of LM based on the staging system. However, it is essential that the use of the classification is only when the metastases appear after the primary tumor has been resected and, at restaging, it is cold on positron emission tomography (PET).

The second modification of the proposal is rooted in two previous papers and reflects our current thinking [12,13]. The proposal classification system should reflect clinical processes underlying the development of PMs and should be independent of the primary tumor type. To avoid confusion with the TNM descriptors used for primary tumors, we propose a 'PMTNM' system, where PM stands for pulmonary metastasis (see Table 1). While we exclusively focus on PMs in this paper, the simplicity of the methodology allows it to be tweaked and expanded to describe other, nonpulmonary metastases (for example, bmTNM for brain metastases, lmTNM for liver metastases, etc.).

T descriptor

This initial descriptor is rooted in the number of PMs that can be detected. Because the disease is known to be invasive, the T levels are better suited to describe the number of PMs that can be detected: T1 (1 PM), T2 (2–3 PMs), T3 (>3 PMs). This may be followed by a small-case indication of laterality (only for T2 and T3), such

Table 1. Definition for PMTNM descriptors.

Descriptor	Definition
m	Metachronous
s	Synchronous
T	PM (n)
T1	1 PM
– T2	2 or 3 PMs
– T2a	2 or 3 PMs, unilateral
– T2b	2 or 3 PMs, bilateral
T3	>3 PMs
– T3a	>3 PMs, unilateral
– T3b	>3 PMs, bilateral
N	Lymph node involvement
– NX	Unknown lymph node status
– N0	No lymph node involvement
– N1	Involvement of the hilar lymph nodes
– N2	Involvement of the mediastinal lymph nodes
– N3	Contralateral involvement of the mediastinal lymph nodes (only for unilateral lung metastasis T1, T2a or T3a)
M	Other, nonpulmonary metastases
– M0	No other, nonpulmonary metastasis
– M1	1 nonpulmonary metastatic site
– M2	>1 nonpulmonary metastatic site

a: Unilateral; b: Bilateral; n: Number; PM: Pulmonary metastases; TNM: Tumor node metastasis.

as "a" for unilateral presentation and "b" for bilateral presentation. It is debatable whether to set a clear cutoff point in terms of the number of PMs, but most authors would agree that fewer than three lesions are frequently reported as a convincing prognostic factor for better survival, even in the absence of a consensus about a definite, reliable predictor. The advantage of this classification is that it reconciles both the proponents of single versus multiple PM and those of the oligometastatic state, an ill-defined, yet useful notion [14]. Overall, and in spite of the various ways to measure risk and prognosis, there seems to be agreement that a single PM is a better prognostic factor for 5-year overall survival than more than one PM. The disease-free interval has been also reported as a prognostic factor, but the interval time was not uniformly reported in most series, which is why we decided to simplify and add only the time of diagnosis [7,8].

N descriptor

The N descriptor describes the lymph node involvement. NX (unknown lymph node involvement), N0 (no lymph node involvement), N1 (hilar lymph node involvement) and N2 (mediastinal lymph node involvement) are possible categories. In the case of unilateral lung metastases (namely PMT1, PMT2a or PMT3a), N3 should also be considered (contralateral nodal involvement). Various studies report hilar or mediastinal lymph node involvement as an important prognostic factor of worse outcomes [9]. In particular, some studies indicate that the mere fact that any lymph node might be invaded is in itself a negative predictor. As such, one could again argue for a simpler scale (N0/N1 only), but for the sake of completeness, we suggest differentiating these situations along anatomical lines. Notably, a number of authors resort to lymph node involvement to make the surgical versus nonsurgical treatment decision, although they caution that even some patients with intrathoracic lymph node metastases have a longer overall survival with surgery than with chemotherapy alone [9]. Most authors today would agree that lymph node assessment during the operation is important for prognosis and perhaps to increase the survival rate for patients.

M descriptor

The M descriptor describes the presence and location of other, nonpulmonary metastases. It spans from M0 (no other metastasis) to M1 (another nonpulmonary metastatic site) and M2 (more than one nonpulmonary metastatic site). Due to the wide array of possible nonpulmonary metastases, this descriptor would almost certainly carry less significance than the other two, with the possible exception of hepatic metastases found in patients with a primary

Table 2. Stage grouping descriptors.

Stage grouping descriptor	PMTNM stages included
Stage 1	m PMT1–2a N0 M0
Stage 2	s PM T1–2a N0M0
	m or s PMT2b–T3a N0 M0
Stage 3	m or s PMT1–3a N1–2 M0–1
Stage 4	Any T3b
	Any N3
	Any M2

PM: Pulmonary metastases; TNM: Tumor node metastasis.

colorectal cancer (CRC) tumor. While this is a very specific presentation, the frequency of CRC and its tendency to seed metastases in the lungs and liver justifies attention.

Stage groupings

In order to simplify matters, we complete the proposed staging scale with groupings (Table 2), much like the TNM scale used for primary tumors. This allows not only a fine classification of PMs but also a wider grouping to identify general tendencies in the long run. We suggest as follows: mT1 or mT2a N0 M0 (group stage 1), sT1–T2a, m or sT2b T3a N0 M0 (group stage 2), m or sT1–3a N1–2 M0–1 (group stage 3) and any T3b, N3 or M2 (group stage 4).

Discussion

In 1998, Pastorino *et al.* proposed a staging proposal for PMs based on the analysis of the International Registry of Lung Metastases [15]. They included only three clinical parameters (complete resection, disease-free interval of 36 months and number of metastases) and elaborated four distinct stage groups. Hirosawa *et al.* developed a prognostic staging system using a pulmonary stage for pulmonary metastases in patients with CRC [16]. They identified four clinical factors (number of metastases, distribution uni/bilateral, disease-free interval between primary tumor and pulmonary metastases and hilar or mediastinal lymph node involvement) and were able to classify patients into three groups (grades A to C) with good prediction of the prognosis of survival. However, their classification is not routinely used in clinical practice and is only focused on patients with CRC. One possible limitation of this stratification by initial tumor location is that many such tumors tend to metastasize in various locations. This is the basis for the decision to define our classification scheme based on the metastatic location instead.

Similar reasoning led a group of authors to publish a recent paper on a central notion, that of the oligometastatic state, defined in their case as three to five metastases [14]. These authors explored this notion and designed a classification system with nine possible outcomes, depending on the exact clinical presentation. This is aligned with our own proposal both in spirit and in terms of the number of lesions (we chose a conservative approach by limiting them to three lesions).

In a recent paper, we explained in detail the rationale for including the number of mediastinal nodal involvements in the dedicated staging system [13]. The reason is the evidence that positive node N1 or N2 adversely affects survival in patients undergoing LM [17,18]. Surgeons from the Mayo clinic stated that there is no doubt that prognosis is impaired by additional node involvement and the best practice is to exclude these patients from lung surgery [19]. Increase uncertainty, some authors did not find differences in survival in patients with LM secondary to renal cancer and mediastinal nodal involvement [20], but this could be due to different sampling or extended dissection techniques that can vary between surgeons [21]. Certainly, the extent of lymphadenectomy (sampling or extended), the type of approach (video-assisted thoracoscopic surgery [VATS] or open) and the type of lung resection (segmentectomy, lobectomy, wedge or with laser precision technique) could influence survival, and therefore further discussion is needed. However, the well-known TNM staging system does not consider all of these factors.

We understand that the classification suggested here might make the description of PMs complex, but it might also be a step forward in allowing for finer analysis of end points. Yet, the real value of such a staging system is elsewhere. By sorting PMs by type and presumably, biology, we hope to allow future studies to explore predictive factors and survival prognosis factors with enough nuance so that clear evidence will emerge on at least one or

two aspects. Part of what makes it difficult to properly manage PMs is that too many conditions, biological natures and characteristics are lumped together into a single, over-simplified label. The current proposal does not account for tumor biology. While striving to keep some simplicity in the overall definition of groups, it does not take into account the biology of the primary tumor (epithelial vs sarcomatous tumors) which is one of the major criticisms expressed for the original TNM system for primary tumors [21]. But, as we are promoting the classification, for clarity and simplicity, we think it is too early to include the histology of the primary tumor.

Moreover, as the cutoff for disease-free survival is unclear in the literature, we prefer to differentiate only metachronous and synchronous metastases (MTS). Our initial attempts [12] were to classify PMs and was a step in the right direction; herein we refined our last TNM classification [13] and report the stage groups (Table 2) [12]. Of course, careful, detailed analysis and application of the TNM of various databases is necessary in order to validate the proposal. Only then will the classification achieve its goal to discern an increasing number of details and differences, leading to the definition of an increasing number of subgroups.

The major goal of a staging system for PMs, which has been reported by us previously [12,13], is to identify patients who will benefit from LM and separate them from those who will not [5,22]. A side benefit of the classification we propose is that (admittedly smaller) groups of patients will be more homogeneous. This will help to offer all patients the most suitable course of treatment for their exact disease, and also will permit comparison of more homogeneous groups of patients for research purposes [13]. Management of metastatic patients requires serious simultaneous consideration of the site of the metastases and the primary tumor; in case of pulmonary metastases, for practical use, these two classifications, TNM and PMTNM, should be separated. It is not of minor importance that the TNM staging for MTS could easily be transferred to nonpulmonary metastases, such as liver metastases (lmTNM) or brain metastases (bmTNM). We wish to submit our reflections to the community at large and hope that many series will result that use the system and either validate or refine it. We look forward to improvements in the care and the classification of pulmonary metastases.

Conclusion

The TNM staging system for pulmonary metastases will certainly help to find those patients who benefit from lung metastasectomy from those who will not. Moreover, it will allow physicians, oncologists and surgeons to speak the same language in comparing their data and assessing the results of treatment of lung metastases.

Future perspective

The worldwide use of a dedicated staging system for pulmonary metastases will permit the identification of patients who benefit from lung metastasectomy, to separate them from those who will not and, in few words, to personalize treatment [23]. It will also permit the comparison of more homogeneous groups of patients for research purposes. The classification will allow physicians, oncologists and surgeons to speak the same language in comparing their data and assessing the results of treatment of lung metastases. This dedicated classification for pulmonary metastases could also serve to build an international database. Although we are validating this proposal using our database, we hope that many series will use and endorse this classification.

Financial & competing interests disclosure

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Executive summary

Introduction

- Pulmonary metastasectomy is currently proposed for resectable pulmonary disease in operable patients with no other distant lesions.
- Pulmonary metastases have heterogenous clinical presentations that are correlated with the biological aggressiveness of the metastatic disease.
- Here, we update our previous tumor node metastasis (TNM) classification system for pulmonary metastases that is similar to the well-known TNM classification system for cancer.

TNM descriptors & staging

- The T-descriptor expresses the number of detected pulmonary metastases.
- Laterality of the presentation (uni- or bilateral) and the time of presentation (metachronous or synchronous) are also included.
- The N descriptor describes the lymph node involvement.
- The M descriptor describes the presence of other nonpulmonary metastases.

Discussion

- The real value of this proposal is its utility for the exploration of survival prognosis factors with enough nuance, so that clear evidence will emerge on some aspects.
- This proposal classifies pulmonary metastatic patients in homogenous groups, because too many conditions, biological natures and characteristics are lumped together into a single, over-simplified pulmonary metastatic disease descriptor.
- The use of this proposed system could facilitate the precision treatment of pulmonary metastases.

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