

# Proposals for revisions of the classification of lung cancers with multiple pulmonary sites: the radiologist's, thoracic surgeon's and oncologist's point of view

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## Introduction

The primary goal of tumor, node and metastasis (TNM) classification is to provide a nomenclature for tumor extent that creates homogeneous cohorts of tumors.

In the 7<sup>th</sup> Edition of the TNM classification for lung cancer there was some ambiguity about classification of multiple pulmonary sites. An international multidisciplinary subcommittee of the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors committee (SPFC) has therefore proposed a revision of the classification of lung cancers with multiple pulmonary sites, according to the four following categories (1):

- (I) Second primary lung cancers, indicating two different histologic types of malignant pulmonary lesions, synchronous or metachronous, to be staged separately, each with a T, N and M descriptor;
- (II) Separate tumor nodules (intrapulmonary metastases), indicating a typical primary lung cancer, with one separate solid tumor nodule of the same histologic type. Based on the location of the second nodule relative to the primary tumor site, the tumor will be designated as: T3, in the same lobe; T4, in an ipsilateral but different lobe; M1a in the contralateral lung;
- (III) Multifocal lung adenocarcinoma with ground glass/lepidic features, indicating multiple sub-solid nodules on CT examination. In this category, T should indicate the number of lesions, and a single N and M category applies to all tumor foci

collectively;

- (IV) Pneumonic-type of lung adenocarcinoma, indicating a diffuse consolidative pattern without proximal bronchial obstruction.

## The radiologist's point of view

Changes in TNM staging for lung cancer have conditioned diagnosis and treatment of patients over time. For example, in 1993 the presence of multiple nodules used to raise the T category by one when in the same lobe while it raised T-staging to T4, when in a different lobe. In 2010 a separate nodule was classified as T3 for a same-lobe, T4 for an ipsilateral different-lobe, and as M1a for a contralateral nodule.

Since the stage of disease changes treatment, the radiologist should always be updated and aware of the latest version of TNM staging, in order not to incur in misleading reports.

Challenges for the radiologist at staging of lung carcinoma, are due to the overlap of appearances of different pulmonary nodules. Specifically, for the abovementioned four categories:

- (I) Second primary lung cancers. The same CT appearance of different nodules does not establish by itself that the lesions are manifestations of the same tumor. Therefore, the maximum number of CT descriptors should be mentioned (2), in order to facilitate the discrimination of separate or single tumor source. In case of clear differences between nodules, these should be emphasized and the hypothesis of different primary tumors should be clearly stated in the report;

- (II) Separate tumor nodules (intrapulmonary metastases). Nodules may still be part of the same entity, even when they show different patterns of presentation. This may apply for example to nodules of different size, where necrotic changes and intratumoral heterogeneity may mimic different histologies. Moreover, according to different location and size of lesions (3,4), it is not always possible to biopsy all the nodules. In this specific setting, imaging examinations should indicate the highest number of descriptors of malignancy for each nodule, and emphasize similarities/dissimilarities of nodules. Unfortunately, until more detailed studies of the tumoral texture will be recognized (5), the biopsy will remain the only method to assess different histologies;
- (III) Multifocal lung adenocarcinoma with ground glass/lepidic features. The ground glass and solid components seen by CT generally correspond to lepidic and invasive histologic patterns, respectively. When reporting these lesions at CT, the lesion size should be given of both the largest diameter of the solid component and the entire lesion, comprising the ground-glass opacity. CT should also indicate the number of lesions;
- (IV) Pneumonic-type of lung adenocarcinoma. Invasive mucinous adenocarcinoma shows a mixture of radiological features, corresponding to the underlying histological subtypes. These tumors typically present without nodal or systemic metastases despite diffuse pulmonary involvement and this may sometimes be a distinctive sign.

### The thoracic surgeon's point of view

Indications to curative lung cancer resection strictly relies on TNM staging and—following TNM modifications and updates—surgical indications to lung cancer treatments have been gradually modified and mainly expanded in the last years.

With the introduction of the abovementioned updates, surgery may play a more active role in lung cancer treatment, as following described:

- (I) Second primary lung cancers. The new staging proposal—both in synchronous and metachronous cases—allows a local treatment that may be represented by a two-steps resection (in fit patients after an adequate cardiopulmonary assessment)

or by combined surgical and stereotactic body radiation therapy (in patients with border line cardiopulmonary function) (6);

- (II) Separate tumor nodules (intrapulmonary metastases). The presence of a second lesion in a different lobe, ipsilateral to a primary lung cancer that may be radically resected by standard lobectomy, may be treated with a subanatomic resection (e.g., wedge resection). Therefore this is not anymore a contraindication to surgery with radical intent. Moreover, the presence of additional lung nodule(s) in the same lobe can be radically treated by standard lobectomy (7);
- (III) Multifocal lung adenocarcinoma with ground glass/lepidic features. In this subset of patients, surgery may rarely play a curative role because of the multifocal spread of the tumor itself. Nevertheless, when a histological diagnosis is required, and bronchoscopy or CT-guided biopsy are not able to reach none of the target lesions, minimally invasive surgical approach may be advocated as a diagnostic tool. These lesions are very often difficult to locate at palpation, and preoperative localization by CT guided radioisotope injection is recommended (8);
- (IV) Pneumonic-type of lung adenocarcinoma. In this subset of patients, surgery does not play any curative role; considering the local diffusion of the disease and the absence of distant and nodal involvement in this form, bilateral lung transplantation has been advocated in the past. However, due to high recurrence rate, transplantation for this indication remains controversial (9).

### The oncologist's point of view

The treatment of non-small cell lung cancer (NSCLC) has been changing dramatically in the last years, principally based on the identification of different genetic aberrations, as *KRAS*, *EGFR* and *ALK*, that present different incidence among different histological subtypes. Patients presenting druggable mutations as *EGFR* and *ALK*, show a significant improvement in survival, due to the utilization of first-, second- or third-generation of target agents.

Although, the revision of TNM staging of lung cancers with multiple sites appears to have a limited significance for the oncological treatment, it may allow a better management of patients with multiple nodules:

- (I) Second primary lung cancers. A multidisciplinary

approach is necessary to evaluate every different primary lung cancer. Generally, this pattern is characterized by different lung lesions with similar pathological features. A histopathological evaluation is mandatory on T and N components, where the two T evaluations differ. Evaluation of *EGFR* and *ALK* alterations should be considered in patients with lymph nodal involvement. However, in patients with two different primary lung cancers, with no lymph nodal involvement, there is no indication for induction chemotherapy;

- (II) Separate tumor nodules (intrapulmonary metastases). NSCLC harboring *EGFR* mutations or *ALK* translocation frequently show as small lung nodules. In these cases, if possible, biomarkers analysis should be performed: in case of M1a disease positive to druggable mutations, target agents should be considered, especially if local treatment is not feasible;
- (III) Multifocal lung adenocarcinoma with ground glass/lepidic features. Histopathologic evaluation of these pulmonary lesions is essential. Evaluation of oncological treatments should be considered only for disseminated bilateral lung lesions. Adenocarcinoma with ground-glass opacities (GGO) present rare incidence of *ALK* translocations. Different studies have evaluated the incidence of *EGFR* mutations and GGO, confirming that there is no significant association between GGO and *EGFR* mutations (10-16);
- (IV) Pneumonic-type of lung adenocarcinoma. Staging and treatment evaluation for this particular type of lung cancer should follow the usual guidelines for the treatment of NSCLC. In patients with this histopathological diagnosis, *EGFR* mutation analysis should be considered as mandatory. Indeed, *EGFR* mutations appear to be significantly high in this histological subtype (17).

## Conclusions

The new proposal for revision of the classification of lung cancers with multiple pulmonary sites, according to four different categories, should help in choosing the proper treatment for patients with multiple tumor nodules. However, some ambiguities in differentiating same or different entities still exist, especially in the first two categories, in case histological examination cannot be performed.

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## Footnote

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