ORIGINAL ARTICLE

The IASLC Lung Cancer Staging Project: Summary of Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification

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ABSTRACT

Introduction: Patients with lung cancer who harbor multiple pulmonary sites of disease have been challenging to classify; a subcommittee of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee was charged with developing proposals for the eighth edition of the tumor, node, and metastasis (TNM) classification to address this issue.

Methods: A systematic literature review and analysis of the International Association for the Study of Lung Cancer database was performed to develop proposals for revision in an iterative process involving multispecialty international input and review.

Results: Details of the evidence base are summarized in other articles. Four patterns of disease are recognized; the clinical

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***See Appendix for the members of the IASLC Staging and Prognostic Factors Committee, Advisory Boards, and the Multiple Pulmonary Sites Workgroup.*

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presentation, pathologic correlates, and biologic behavior of these suggest specific applications of the TNM classification rules. First, it is proposed that second primary lung cancers be designated with a T, N, and M category for each tumor. Second, tumors with a separate tumor nodule of the same histologic type (either suspected or proved) should be classified according to the location of the separate nodule relative to the index tumor—T3 for a same-lobe, T4 for a same-side (different lobe), and M1a for an other-side location—with a single N and M category. Third, multiple tumors with prominent ground glass (imaging) or lepidic (histologic) features should be designated by the T category of the highest T lesion, the number or *m* in parentheses (#/m) to indicate the multiplicity, and a collective N and M category for all. Finally, it is proposed that diffuse pneumonic-type lung cancers be designated by size (or T3) if in one lobe, T4 if involving multiple same-side lobes, and M1a if involving both lungs with a single N and M category for all areas of involvement.

Conclusion: We propose to tailor TNM classification of multiple pulmonary sites of lung cancer to reflect the unique aspects of four different patterns of presentation. We hope that this will lead to more consistent classification and clarity in communication and facilitate further research in the nature and optimal treatment of these entities.

Keywords: Lung cancer; Non–small cell lung cancer; TNM classification; Lung cancer staging; Multiple tumors

Introduction

The seventh edition of the tumor, node, and metastasis (TNM) classification for lung cancer contained some ambiguity with respect to classification of lung cancer with multiple pulmonary sites of involvement. Surveys of experts reveal that there was marked variability in how different people would classify particular tumors,[1,2] thus undermining the primary goal of TNM classification, which is to provide a nomenclature for tumor extent that creates homogeneous cohorts of tumors. Furthermore, the heterogeneity resulting from this variability hampers the ability to interpret research studies.

Defining homogeneous groups is particularly important among patients with multiple pulmonary sites of lung cancer, as several patterns of presentation are associated with multiple lesions. These exhibit marked differences in biologic behavior, including survival and recurrence patterns. The heterogeneity in classification since the seventh edition of the TNM classification has arisen both from a lack of clear distinction between disease entities and from ambiguity about how to apply stage classification rules to these patients.

Second primary lung cancers have long been recognized by the TNM system, although little detail was provided regarding how this diagnosis should be established. Separate tumor nodules were classified as M1 until 1993, when they were defined as raising the T category by 1 when in the same lobe as the primary and as T4 if in a different lobe. In 1997 a separate tumor nodule was classified as T4 if in the same lobe and M1 if in a different lobe (ipsilateral or contralateral). In 2010 these were reclassified as T3 for a same-lobe separate nodule (and the term *satellite* nodule for such lesions was abandoned), as T4 for an ipsilateral different-lobe nodule, and as M1a for a contralateral nodule. Moreover, previous editions of the TNM classification provided little guidance on what constitutes a separate tumor nodule until the seventh edition, in which the language has turned out to be variously interpreted.[1,2] Furthermore, the seventh edition contains only vague mention of ground glass or lepidic lesions, and it predated the 2011 definition of adenocarcinoma subtypes.[3,4]

To provide better clarity for the eighth edition of the TNM classification, an international subcommittee of experts conducted a comprehensive review of relevant data. This was used to identify distinct patterns of disease and to develop criteria to categorize lung cancer with multiple pulmonary sites of involvement accordingly. Furthermore, the subcommittee formulated clear instructions on how to apply the TNM classification rules to each pattern of disease, taking into account the particular issues that each one presents. The full scope of this process is detailed in additional articles.[5–7] This article summarizes the recommendations for lung cancer with multiple pulmonary sites of involvement in one document.

Four patterns of presentation are associated with multiple pulmonary sites of lung cancer (Fig. 1). First, patients can present with second primary lung cancers. The demographic characteristics, outcomes, and recurrence patterns for each tumor are similar to those of single "typical" lung cancers according to the stage and histologic type. Second, some patients with a solid primary lung cancer have one or more separate solid tumor nodule(s) of the same histologic type (referred to as intrapulmonary metastasis in the pathology community). The behavior of these tumors is similar to that of a similar solitary tumor; outcomes are slightly inferior and affected by how they are treated. A third pattern of disease involves patients presenting with multiple lung cancer nodules with prominent ground glass or lepidic (GG/L) features. This group has different demographic characteristics, excellent outcomes, and infrequent recurrences outside the lung parenchyma. A fourth pattern of disease involves a form of lung cancer that is radiologically similar to a pneumonia (so-called pneumonic-type lung cancer). Extrathoracic and nodal

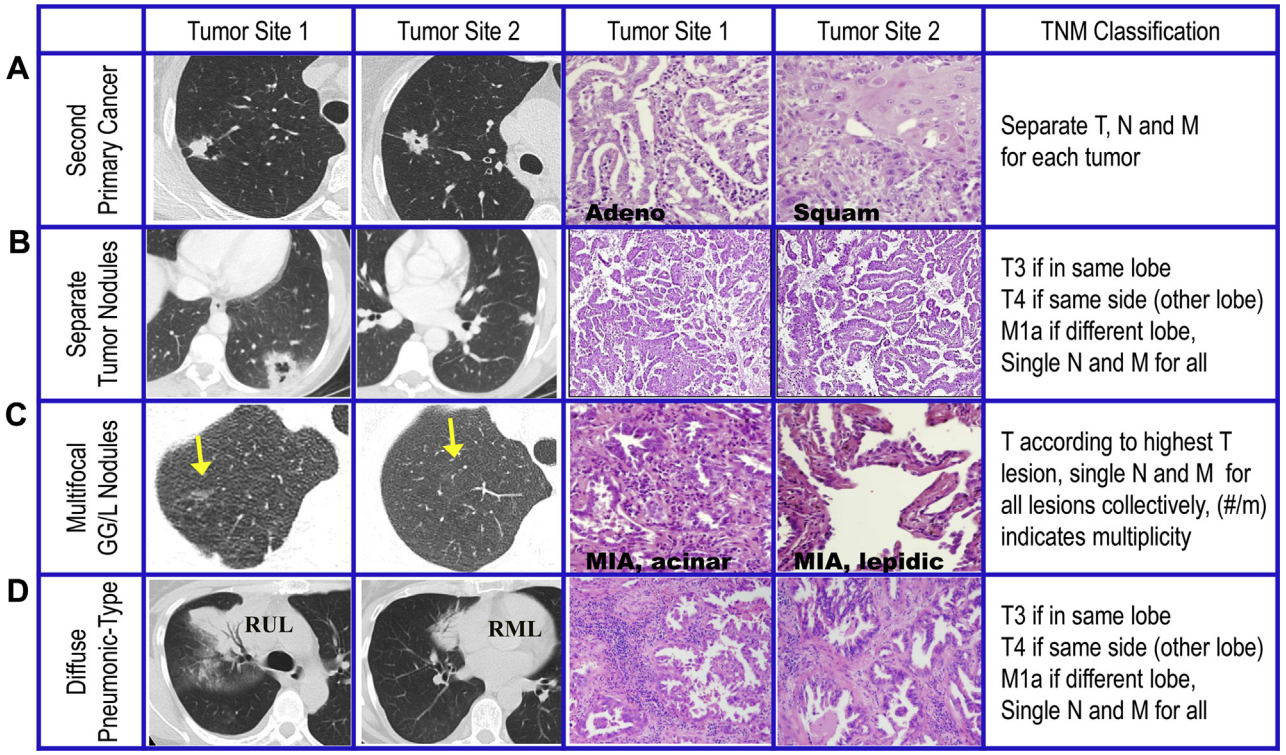

Figure 1. Representative examples of four patterns of disease that manifest multiple pulmonary sites of lung cancer. (*A*) Second primary cancers. A patient with two primary lung cancers in the RUL. CT images of each in the left two panels; corresponding microscopic images showing an adenocarcinoma and a squamous carcinoma in the next two panels. Note that most second primary cancers are of the same (not a different) histologic type. (*B*) Separate tumor nodules. A patient with a separate tumor nodule of the same histotype as the index tumor. The left panels show CT images of each lesion; the right panels show the corresponding microscopic images. (*C*) Multifocal GG/L lung cancer. A patient with multifocal GG/L tumors in the right upper lobe (who had other GG/L tumors in other lobes). Arrows point to two GG/L tumors on CT in the left two panels; the next two panels show corresponding microscopic images (both were adenocarcinoma with a prominent lepidic component, although with different other adenocarcinoma subtypes). These tumors are classified together as GG/L tumors regardless of such secondary differences. (*D*) Pneumonic-type lung cancer. A patient with pneumonic-type lung cancer (this patient also had focal sites of disease in the RLL). The left panels show CT images of the RUL and RML with the typical regional areas with a ground glass and consolidative appearance; the next panels show the corresponding microscopic images. Adeno, adenocarcinoma; CT, computed tomography; GG/L tumors, tumors with prominent ground glass (imaging) or lepidic (histologic) features; MIA, minimally invasive adenocarcinoma; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; Squam, squamous cell carcinoma.

involvement is infrequent, but the prognosis is distinctly worse than that for patients with multiple GG/L nodules.

Methods

To develop proposals for revision of the classification of lung cancers with multiple pulmonary sites of involvement, an international multidisciplinary subcommittee of the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee (SPFC) was formed. This group (i.e., the authors of this article) conducted a comprehensive review of the relevant literature. Details of this process and results are provided in a series of review articles[5–7]; a summary of these data is provided in the next section of this article. In addition, the IASLC database from 1999 to 2010 was analyzed regarding separate tumor nodules (this was the only pattern of disease for which there were sufficient data in the database). This evidence was then used in an iterative process to develop recommendations. These documents were critically evaluated by an extended workgroup (see the Appendix), in addition to review and eventual endorsement by the entire SPFC.

Results

Brief Summary of Evidence Review

Second Primary Lung Cancers. A different histologic type is generally sufficient to establish two malignant pulmonary lesions as separate primary cancers, provided that adequate tissue is available. Similarly, different appearance by a detailed histologic assessment (proportion of subtypes, grade, cytologic and stromal features, etc.) of resected specimens can establish tumors

as second primary cancers. However, the same (or predominant) histologic type does not by itself clearly establish that the lesions are manifestations of the same tumor. Historical studies, clonality studies, and outcomes studies indicate that the large majority of second cancers of the same histologic type are likely to be second primary lung cancers.[6] Similarly, the same morphologic appearance by a more detailed histologic assessment as already noted should not be taken by itself as clear evidence that two lesions are manifestations of the same tumor; it is only suggestive that two lesions may be related.[6]

Assessment of biomarkers (driver gene mutations) is only suggestive, as there is a substantial rate of discordance among different samples of the same tumor and concordance among clearly separate tumors.[6] Thus, mutational profiling should not be considered definitive and must be considered together with other information. More detailed genetic assessments (comparative genomic hybridization, Next-Gen sequencing) are promising but not sufficiently studied or standardized, and are they complex to use in routine clinical practice.[6]

Separate Tumor Nodules (Intrapulmonary Metastasis). The IASLC database for the seventh (1990–1999) and eighth (1999–2010) editions each included a small proportion of patients who were recorded as having a separate malignant nodule (2.5% and 3.5%, respectively).[8,9] It appears that these patients primarily fit a pattern of disease consisting of a typical primary lung cancer (i.e., a solid mass) with a separate solid tumor nodule of the same histologic type (rarely more than one). The outcomes of these patients in the IASLC database analysis were consistent with those gathered in a systematic literature review.[5]

Among clinically staged patients, overall survival (OS) decreased progressively by location of the separate tumor nodule relative to the primary tumor (same lobe > same lung [different lobe] > other lung),[5] which is consistent with the analysis for the seventh edition. However, OS seems to have been primarily affected by the treatment given; there was no difference in OS by separate tumor nodule location among only surgically managed patients or among nonsurgically managed patients. Other confounding factors include varying proportions of incidentally discovered nodules (not identified preoperatively) and selection factors leading some patients to be managed surgically and others nonsurgically. Because of an inability to separate the influence of these various factors, the TNM classification of the seventh edition for separate tumor nodules was maintained.

Multifocal Lung Adenocarcinoma with Ground Glass/Lepidic Features. An increasing number of patients with lung cancer are being encountered who have multiple subsolid nodules (either pure ground glass or part solid) on computed tomography (CT) examination. The pathologic correlates of this appearance are lepidic-predominant adenocarcinoma (LPA), minimally invasive adenocarcinoma (MIA), or adenocarcinoma in situ (AIS) with or without other subtypes of adenocarcinoma as lesser components.[3] The ground glass and solid components seen by CT generally correspond to lepidic and invasive histologic patterns, respectively. The nature of these lesions and their relationship to one another are not yet fully understood; they are viewed as separate tumors with an in situ or invasive component that has arisen from a predominant noninvasive component. The results of clonality studies comparing multiple such tumors in the same patient are conflicting.[7]

The patients with such lung adenocarcinomas that present as multiple nodules with ground glass features have a decreased propensity for nodal or systemic spread and an increased propensity to the development of additional subsolid cancers.[7] Furthermore, they often exhibit a more indolent behavior.[7] There are often numerous additional GG/L foci, and the patients are often women and nonsmokers. These lesions are easy to recognize clinically (by CT imaging) and pathologically (by a prominent lepidic component). Thus, this pattern of disease has many distinct features.

Pneumonic-Type Lung Adenocarcinoma. A subset of patients exhibits a diffuse consolidative pattern (a "pneumonic type" of lung adenocarcinoma) without proximal bronchial obstruction.[10–12] There are typically areas of ground glass as well as solid consolidation. This pattern of clinical presentation typically correlates with invasive mucinous adenocarcinoma,[4] which characteristically shows a goblet and/or columnar cell morphologic pattern with abundant intracytoplasmic mucin. Although invasive mucinous adenocarcinoma often shows lepidic-predominant growth, extensive sampling usually reveals invasive foci, sometimes with desmoplastic stroma. Invasive mucinous adenocarcinoma may show a heterogeneous mixture of adenocarcinoma subtypes. Surrounding alveolar spaces often fill with mucin. This heterogeneous histologic appearance is frequently similar throughout areas of involvement in a particular patient. A detailed study of a patient with diffuse pneumonic adenocarcinoma suggested different clonality in each of the five lobes examined[13]; how to interpret this case is controversial. Most of these patients have an invasive mucinous adenocarcinoma, the rest have mixed or nonmucinous adenocarcinomas.[7]

These patients typically present without nodal or systemic metastases despite diffuse pulmonary involvement; the occasional use of double-lung transplantation

as a treatment underscores this.[14–16] Although the rate of progression is often slow, survival is markedly worse than for patients with GG/L tumors. Thus, although there are some similarities between the multiple GG/L pattern of disease and the pneumonic pattern of disease (e.g., ground glass and lepidic components, decreased propensity for nodal and systemic involvement), there are sufficient differences to consider this a distinct pattern of disease.

Recommendations for Second Primary Lung Cancers

Description. The criteria to identify two tumor foci as either separate primary tumors or related (i.e., arising from a single source) are summarized in Table 1. Some criteria are generally definitive by themselves, whereas others are suggestive but must be considered together with all available information. The relative weight to give to a particular suggestive observation will depend on several factors such as the degree of similarity or difference, the reliability of the assessment, and what data are available (e.g., the extent of prior imaging available, amount of tissue available–i.e. a limited biopsy or resection specimen). It is easier to define criteria that identify two malignancies as separate than to define criteria that conclusively establish that the tumors are identical. Ideally, a decision to classify two (or more) lesions as synchronous primary cancers or two identical foci of a single cancer should be based on the judgment of an experienced multidisciplinary team, taking into account all factors (e.g., clinical, imaging, histologic, etc.).

Proposed TNM Classification. Two (or more) synchronous primary lung cancers should be classified separately, each with a T, N, and M descriptor (i.e., a T, N, and M for one tumor and another T, N, and M for the other tumor). For example, a patient with a 2.2-cm squamous cell cancer in the right upper lobe, a 3.5-cm adenocarcinoma in the left upper lobe with adenocarcinoma in a L11 node that was discovered by endobronchial ultrasound aspiration, and no other evidence of nodal or systemic metastases should be classified as having a T1c N0 M0 squamous cell cancer and a T2a N1 M0 adenocarcinoma.

This TNM classification of tumors judged to be second primary lung cancers should be applied to both synchronous and be used metachronous second primary lung cancers, and be used whether the two primary tumors are in different lungs, different lobes, or in the same lobe. Furthermore, this classification should be applied to synchronous primary lung cancers recognized clinically or grossly as well as to those recognized only on pathologic examination.

Recommendations for Separate Tumor Nodule (Intrapulmonary Metastasis)

Description. Patients should be classified as having separate tumor nodule(s) when there is a "classic" lung cancer (i.e., solid, spiculated) and one (or more) solid separate lung nodules, either presumed (clinical staging) or proved (pathologic staging after comprehensive histologic assessment) to be metastatic from the primary lung cancer; the criteria are summarized in Table 2.

Table 1. Criteria to Distinguish Second Primary versus Related Tumors

Clinical criteria[a]
Tumors may be considered second primary tumors if
They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma) by biopsy.
Tumors may be considered to be arising from a single tumor source if
Exactly matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors
Different radiographic appearance or metabolic uptake
Different biomarker pattern (driver gene mutations)
Different rates of growth (if previous imaging is available)
Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source
Same radiographic appearance
Similar growth patterns (if previous imaging is available)
Significant nodal or systemic metastases
Same biomarker pattern (and same histotype)
Pathologic criteria (i.e., after resection)
Tumors may be considered second primary tumors if
They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma).
They are clearly different by a comprehensive histologic assessment.
They are squamous carcinomas that have arisen from carcinoma in situ.
Tumors may be considered to be arising from a single tumor source if
Exactly matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors (to be considered together with clinical factors)
Different biomarker pattern
Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source (to be considered together with clinical factors)
Matching appearance on comprehensive histologic assessment
Same biomarker pattern
Significant nodal or systemic metastases

[a]A comprehensive histologic assessment is not included in clinical staging, as it requires that the entire specimen has been resected.

Table 2. Criteria to Categorize a Lesion as a Separate Tumor Nodule (Intrapulmonary Metastasis)

Clinical criteria
Tumors should be considered to have a separate tumor nodule(s) if
There is a solid lung cancer and a separate tumor nodule(s) with a similar solid appearance and with (presumed) matching histologic appearance.
• This applies whether or not a biopsy has been performed on the lesions, provided that there is strong suspicion that the lesions are histologically identical.
• This applies whether or not there are sites of extrathoracic metastases.
AND provided that
The lesions are NOT judged to be synchronous primary lung cancers.
The lesions are NOT multifocal GG/L lung cancer (multiple nodules with ground glass/lepidic features) or pneumonic-type lung cancer.
Pathologic criteria
Tumors should be considered to have a separate tumor nodule (intrapulmonary metastasis) if
There is a separate tumor nodule(s) of cancer in the lung with a similar histologic appearance to a primary lung cancer.
AND provided that
The lesions are NOT judged to be synchronous primary lung cancers.
The lesions are NOT multiple foci of LPA, MIA, or AIS.

Note: A radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things.
AIS, adenocarcinoma in situ; GG/L, ground glass/lepidic; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma.

Typically there is one additional nodule, although there may be more than one.

However, the designation of separate tumor nodule(s) should not be used if it is judged that the patient has synchronous primary lung cancers (as defined in the previous section). Furthermore, the designation of separate tumor nodule(s) should not be used in patients with multifocal GG/L lung adenocarcinoma (multiple nodules with ground glass features or multiple foci of LPA, MIA, AIS [see the next section]).

Proposed TNM Classification. The TNM classification of a separate tumor nodule(s) (of the same histologic type) is assigned on the basis of location of the nodule relative to the primary tumor site. If it is in the same lobe, the tumor is designated as T3; if in the same lung (different lobe), as T4; and if in the contralateral lung, as M1a.[5] This applies regardless of whether there is involvement of nodal sites or distant (extrathoracic) sites. In other words, such separate tumor nodules in the lung determine the T category even when there are many sites of extrathoracic metastases (but the tumor would be classified as M1b or M1c because of the extrathoracic metastases). Finally, this classification should be applied to separate tumor nodules recognized clinically or grossly as well as to those recognized only on pathologic examination.

Recommendations for Multifocal Lung Adenocarcinoma with Ground Glass/Lepidic Features

Description. Patients with this pattern of disease present with multiple subsolid tumor nodules (either pure ground glass nodule [GGN] or a part-solid nodule). A GGN is a focal nodular area of increased lung attenuation on CT, including both well-defined and poorly defined lesions, through which normal parenchymal structures, including airways and vessels, can be visualized.[17] A subsolid nodule can be either purely ground glass or a part-solid nodule (usually still >50% ground glass but with a solid component). (Note that a radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things.[4])

Tumors should be categorized as multifocal lung adenocarcinoma if there is a malignant subsolid nodule (either suspected or proved) and other nodules with ground glass features, regardless of whether a biopsy has been performed on the other lesions, and if a biopsy has been performed, regardless of whether they are shown to be LPA, MIA, or AIS (Table 3).[7] Frequently, multifocal patients with lung adenocarcinoma have three to 10 (or more) nodules. This categorization should also apply to patients in whom a subsolid lesion appears to have arisen from a GGN (or a lepidic background) but in whom the lesions have become more than 50% solid (or invasive), provided that other nodules with ground glass features are present as well.

Multifocal lung cancer is essentially seen only as a manifestation of adenocarcinoma. The pathologic designation of multifocal lung cancer should be used when there are multiple resected lesions that are either LPA, MIA, or AIS with or without other subtypes of adenocarcinoma as lesser components. It is appropriate to combine pathologic identification of one focus of LPA, MIA, or AIS with clinical information indicating that there are other, nonresected subsolid nodules (e.g., in other lobes). The GG/L category should be used whether a detailed histologic assessment (i.e., proportion of subtypes, etc.) shows the lesions to have a matching appearance or to be different.

Table 3. Criteria to Categorize a Tumor as Multifocal GG/L Adenocarcinoma

Clinical criteria
Tumors should be considered multifocal GG/L lung adenocarcinoma if
There are multiple subsolid nodules (either pure ground glass or part solid), with at least one suspected (or proved) to be cancer.
• This applies whether or not a biopsy has been performed of the nodules.
• This applies if the other nodules(s) are suspected to be AIS, MIA, or LPA.
• This applies if a nodule has become >50% solid but is judged to have arisen from a GGN, provided that there are other subsolid nodules.
• GGN lesions <5mm or lesions suspected to be AAH are not counted.
Pathologic criteria
Tumors should be considered multifocal GG/L lung adenocarcinoma if
There are multiple foci of LPA, MIA, or AIS.
• This applies whether a detailed histologic assessment (i.e., proportion of subtypes, etc.) shows a matching or different appearance.
• This applies if one lesion(s) is LPA, MIA, or AIS and there are other subsolid nodules of which a biopsy has not been performed.
• This applies whether the nodule(s) are identified preoperatively or only on pathologic examination.
• Foci of AAH are not counted.

Note: A radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things.
AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; GG/L, ground glass/lepidic; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma.

The multifocal GG/L lung adenocarcinoma designation should not be applied to patients with multiple GGNs that are thought to all represent benign or preneoplastic lesions (i.e., atypical adenomatous hyperplasia). Pure 5-mm or smaller GGNs and foci of atypical adenomatous hyperplasia should not be counted, although such lesions are often present in patients with multifocal GG/L adenocarcinoma.

Proposed TNM Classification. Multifocal GG/L adenocarcinoma should be classified by the T category of the lesion with the highest T along with the number of lesions (#) or simply (m) for multiple indicated in parentheses, and an N and M category that applies to all of the multiple tumor foci collectively—for example, T1a(4) N0 M0. The apparent decreased propensity for nodal and distant metastases and increased propensity for additional lung lesions supports the concept of a single N and M for all of the pulmonary lesions. The lesion size is determined by the largest diameter of the solid component (by CT) or the invasive component (under a microscope); a designation of Tis should be used for AIS and T1a(mi) for MIA.[18]

The T(#/m) multifocal classification should be applied equally whether the lesions are in the same lobe or in different ipsilateral or contralateral lobes. Furthermore, the T(#/m) multifocal classification should be applied to both grossly recognizable lesions and to those that are discovered only on pathologic examination (microscopically or otherwise).

Recommendations for Diffuse Pneumonic-Type Lung Adenocarcinoma

Description. The category pneumonic-type lung adenocarcinoma refers to tumors with a consolidative pattern

Table 4. Criteria to Categorize a Tumor as a Pneumonic-Type Adenocarcinoma

Clinical criteria
Tumors should be considered pneumonic-type adenocarcinoma if
The cancer manifests in a regional distribution, similar to a pneumonic infiltrate or consolidation.
• This applies whether there is one confluent area or multiple regions of disease. The region(s) may be confined to one lobe, in multiple lobes, or bilateral, but it should involve a regional pattern of distribution.
• The appearance of involved areas may be ground glass, solid consolidation, or a combination thereof.
• This can be applied when there is compelling suspicion of malignancy whether or not a biopsy has been performed of the area(s).
• This should not be applied to discrete nodules (i.e., GG/L nodules).
• This should not be applied to tumors causing bronchial obstruction with resultant obstructive pneumonia or atelectasis.
Pathologic criteria
Tumors should be considered pneumonic-type adenocarcinoma if
There is diffuse distribution of adenocarcinoma throughout a region(s) of the lung, as opposed to a single well-demarcated mass or multiple discrete well-demarcated nodules.
• This typically involves an invasive mucinous adenocarcinoma, although a mixed mucinous and nonmucinous pattern may occur.
• The tumor may show a heterogeneous mixture of acinar, papillary, and micropapillary growth patterns, although it is usually lepidic predominant.

Note: A radiographically solid appearance and the specific histologic subtype of solid adenocarcinoma denote different things.
GG/L, ground glass/lepidic.

by CT (in the absence of an obstructed bronchus), either confined to a particular area (segment or lobe) or diffusely in the lung parenchyma (Table 4). The parenchymal borders of the tumor are infiltrative and typically not well demarcated. The tumor may be confined to one region (e.g., segment, lobe), involve several regions (either confluent or separated), or diffusely involve both lungs. The involved areas typically are a mixture of ground glass and dense consolidation, with frequent air bronchograms radiologically and lepidic and invasive foci microscopically. Most pneumonic-type lung cancers are invasive mucinous adenocarcinomas, the rest are either nonmucinous or mixed mucinous and nonmucinous tumors.

Proposed TNM Classification. In the case of pneumonic-type adenocarcinoma with a single area of tumor, it is straightforward to apply the TNM classification as described for lung cancer in general (e.g., the T category determined by size, and N and M determined by nodal or extrathoracic involvement).[9,19] In the case of multiple pulmonary sites of involvement, the T or M category should be determined by the location of the areas of involvement: T3 if confined to one lobe, T4 if involving different lobes in one lung, and M1a if involving both lungs. If the tumor involves both lungs, the T category should be designated according to the appropriate T category for the side with the greatest amount of tumor (i.e., size or T3 if in one lobe, T4 if in more than one lobe on that side). Because size may be difficult to determine, when the area of involvement extends into an adjacent lobe (as well as a discrete separate area of involvement in an adjacent lobe) the T4 designation should be applied (recognizing extension into another lobe). If the involvement is confined to a single lobe but hard to measure, a designation of T3 should be used. The appropriate N category that applies to all pulmonary sites of the primary tumor collectively is chosen; pleural/pericardial tumor nodules or distant metastases will lead to an M1a, M1b, or M1c designation. The classification should be applied to both grossly recognizable lesions and to those that are discovered only on histologic examination. A detailed histologic assessment to determine whether various areas are exactly matching is not required for pneumonic-type lung cancer.

We propose that the schema for application of TNM classification described for pneumonic-type adenocarcinoma also be used for miliary forms of adenocarcinoma. Because size of miliary involvement is inherently difficult to determine, miliary involvement in a single lobe should be classified as T3 without regard to size.

Discussion

This article summarizes proposals for the eighth edition of the TNM classification of malignant tumors for patients with lung cancer who present with multiple pulmonary sites of involvement (Table 5). Classification of these tumors can be challenging; the goal was to provide definitions with sufficient clarity to lead to consistent classification. The development of these proposals was conducted by a specific subcommittee of the IASLC SPFC according to a formal process involving a systematic review of the relevant literature and an analysis of the IASLC database.

Although a brief summary of background evidence is provided, full details are beyond the scope of this article. A systematic review of the literature regarding the

Table 5. Schematic Summary of Patterns of Disease and TNM Classification of Patients with Lung Cancer with Multiple Pulmonary Sites of Involvement

	Second Primary Lung Cancer	Multifocal GG/L Nodules	Pneumonic-Type Adenocarcinoma	Separate Tumor Nodule
Imaging features	Two or more distinct masses with imaging characteristic of lung cancer (e.g., spiculated)	Multiple ground glass or part-solid nodules	Patchy areas of ground glass and consolidation	Typical lung cancer (e.g., solid, spiculated) with separate solid nodule
Pathologic features	Different histotype or different morphologic features by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)	Same histologic features throughout (most often invasive mucinous adenocarcinoma)	Distinct masses with the same morphologic features by comprehensive histologic assessment
TNM classification	Separate cTNM and pTNM for each cancer	T based on highest T lesion with (#/m) indicating multiplicity; single N and M	T based on size or T3 if in single lobe, T4 or M1a if in different ipsilateral or contralateral lobes; single N and M	Location of separate nodule relative to primary site determines if T3, T4, or M1a; single N and M
Conceptual view	Unrelated tumors	Separate tumors, albeit with similarities	Single tumor, diffuse pulmonary involvement	Single tumor, with intrapulmonary metastasis

AIS, adenocarcinoma in situ; c, clinical; GG/L, ground glass/lepidic; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma; p, pathological; TNM, tumor, node, and metastasis.

definition of second primary lung cancer, outcomes for separate tumor nodules (intrapulmonary metastases), multifocal GG/L lung adenocarcinoma, and pneumonic-type adenocarcinoma, as well as an analysis of the IASLC database, are provided in other articles.[5–7] This evidence informed the proposed criteria for patterns of disease that manifest multiple pulmonary sites of lung cancer and the application of the stage classification system described in this article.

A system of nomenclature to classify anatomic tumor extent cannot be equated to a treatment guideline. Nomenclature can facilitate the discussion of how to treat patients, but patient management is defined by studies specifically focused on particular patients, particular treatments, and the efficacy thereof. Furthermore, the impact of attitudes toward treatment and the prevalence of particular treatment approaches should not be confused with a prognostic impact that is inherent to a tumor characteristic. For example, separate contralateral tumor nodule(s) have been reported to have a poor prognosis. However, almost all of these patients have been managed nonoperatively (i.e., palliatively), although good outcomes are reported after resection (in limited data). Hence, the general prognosis may be more reflective of the attitude toward treatment than an inherent prognostic implication of such nodules per se.[5]

Historically, classification of (and management of patients with) multiple pulmonary sites of lung cancer has been based on speculation primarily about how physical translocation of a malignant cell from one site to another might occur. However, there are now extensive data indicating that the process of metastasis is highly complex, influenced not only by tumor cell–intrinsic genetic and epigenetic determinants but also a complex array of tumor-host interactions at both the primary and metastatic sites.[6,20–22] Tumor cells transform to mesenchymal cells and back again during the process of metastasis; they exist in various states and in permissive niches, and there is a complex bidirectional migration between primary, metastatic, and other sites. This is governed by multiple pathways, cell signaling, and microenvironment characteristics.[6,20–22] Thus, speculative rationale based on routes of physical translocation of tumor cells is refuted by extensive evidence. Terms such as *lymphatic spread* and *hematogenous spread* are based on oversimplified concepts and should not dictate classification or treatment of patients; furthermore, they hamper consideration of the true determinants of metastasis.

Classification inherently involves drawing a line of separation, and there are always borderline zones in which the distinction becomes difficult. Furthermore, there will always be patients with unusual presentations that defy classification. We acknowledge these facts but hope that the structure provided will allow the large majority of patients to be classified easily and consistently and that the guidance provided makes a "best judgment" classification easier in the particularly difficult cases.

Conclusion

This article describes proposed definitions to classify tumors in patients who present with more than one pulmonary site of lung cancer for the eighth edition of the TNM classification. We distinguish several patterns of disease that exhibit multiple pulmonary sites of lung cancer. These are associated with different biologic behavior; defining homogeneous cohorts of tumors requires both clarity about these categories and consistent application of TNM classification rules. Specifically, these patterns of disease involve patients with synchronous primary lung cancers, those with a separate solid tumor nodule(s) (intrapulmonary metastases), multifocal lung cancer presenting as multiple nodules with ground glass/lepidic features, and diffuse pneumonic-type adenocarcinoma. Synchronous primary cancers are classified with a T, N, and M category for each tumor; separate tumor nodules result in a T3, T4, or M1a category depending on the separate nodule's location relative to the primary tumor; multifocal GG/L tumors are classified by the highest T lesion, with the number or *m* for multiple in parentheses (#/m) and an N and M category for all tumor nodules collectively; and for pneumonic-type adenocarcinoma the T component is classified by size or as T3 if in one lobe, as T4 if in two ipsilateral lobes, and M1a if contralateral, with a single N and M category for all sites of pulmonary involvement collectively. These proposals are based on a systematic review of relevant literature, extensive deliberations of an international multidisciplinary expert panel, and several additional levels of review. We hope that this leads to greater ease and consistency in classification of these tumors, while recognizing that there will always be areas of difficulty and tumors that are challenging to classify. We also recognize that the system will need to be refined as further knowledge is gained.

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Appendix

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