ORIGINAL ARTICLE

# The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification

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## ABSTRACT

**Introduction:** Application of tumor, node, and metastasis (TNM) classification is difficult in patients with lung cancer presenting as multiple ground glass nodules or with diffuse pneumonic-type involvement. Clarification of how to do this is needed for the forthcoming eighth edition of TNM classification.

**Methods:** A subcommittee of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee conducted a systematic literature review to build an evidence base regarding such tumors. An iterative process that included an extended workgroup was used to develop proposals for TNM classification.

**Results:** Patients with multiple tumors with a prominent ground glass component on imaging or lepidic component

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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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on microscopy are being seen with increasing frequency. These tumors are associated with good survival after resection and a decreased propensity for nodal and extrathoracic metastases. Diffuse pneumonic-type involvement in the lung is associated with a worse prognosis, but also with a decreased propensity for nodal and distant metastases.

**Conclusion:** For multifocal ground glass/lepidic tumors, we propose that the T category be determined by the highest T lesion, with either the number of tumors or *m* in parentheses to denote the multifocal nature, and that a single N and M category be used for all the lesions collectively—for example, T1a(3)N0M0 or T1b(m)N0M0. For diffuse pneumonic-type lung cancer we propose that the T category be designated by size (or T3) if in one lobe, as T4 if involving an ipsilateral different lobe, or as M1a if contralateral and that a single N and M category be used for all pulmonary areas of involvement.



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

## Introduction

In 1876 Malassez described a bilateral multinodular form of malignant lung tumor.[1] In 1903 Musser described a diffuse infiltrative type of lung cancer involving a single lobe or the entire lung simulating pneumonia.[2] In 1953 the presence of epithelial cells in the alveolar wall was confirmed by electron microscopy[3] and it was realized that neoplastic epithelium may extend along the alveolar surfaces without invasion or destruction of alveolar wall in a pattern referred to as "bronchioloalveolar carcinoma" (BAC).[4,5] The noninvasive pattern of growth along the alveoli was described as "lepidic." For many years BAC was used to describe tumors that contain a lepidic component with or without an additional invasive component. During the last decades of the 20th century, accumulated data indicated that small (<3 cm) single tumors without an invasive component were nearly universally cured by resection.[6] Accordingly, the 1999 and 2004 editions of the World Health Organization (WHO) classification of lung tumors restricted the term *bronchioloalveolar carcinoma* to single purely lepidic tumors without any evidence of invasion.[7,8] However, the new definition was not widely understood or accepted, and in 2011 the term *BAC* was abandoned because it was being used ambiguously in many different contexts.[9]

Lepidic extension of tumor cells permits aeration of the alveoli and results in a characteristic appearance on computed tomography (CT) that is referred to as ground glass. In this review such lesions with prominent ground glass or lepidic features are referred to as ground glass/lepidic (GG/L) nodules. Patients with multiple GG/L nodules are seen fairly commonly, perhaps because of the increasing prevalence of CT imaging; there is at least the perception that multifocal GG/L (or the identification thereof) is becoming more frequent, although the incidence has not been quantified.[10–12]

As in other situations with multiple pulmonary sites of lung cancer, there has been confusion about how to classify tumors with multifocal GG/L nodules.[13,14] The International Association for the Study of Lung Cancer (IASLC) appointed a subcommittee of the Staging and Prognostic Factors Committee (SPFC) to address this and provide greater consistency in classification for the forthcoming eighth edition of the tumor, node, and metastasis (TNM) classification of lung cancer. The full scope of this effort is described in other articles.[15–17] This article reports the work of this subcommittee for multifocal GG/L lung cancer and pneumonic-type lung cancer.

The primary purpose of stage classification is to provide a nomenclature about the anatomic extent of disease to describe homogenous groups of tumors. A consistent nomenclature in turn has many applications (e.g., to describe aspects of the tumor in patients enrolled in clinical trials, as a factor in estimating prognosis after a particular treatment, etc.). It is important to define what is meant by a homogeneous group: the most relevant criterion of homogeneity is to group tumors with a similar biologic behavior attributable to the tumor itself (as opposed to outcomes resulting from patient characteristics or treatment).

Paying attention to disease entities is particularly important for patients with multiple pulmonary foci of lung cancer because the biologic behavior varies dramatically—in terms of outcomes, the patterns of progression, and the issues they present regarding TNM classification. Therefore, the pattern of disease is a crucial aspect in defining homogeneous groups among patients with multiple lung tumors. We have structured our approach according to patterns of disease that are associated with a particular biologic behavior to find the most appropriate TNM nomenclature for each, taking into account the particular issues that each one presents. However, we recognize that it is not entirely clear whether each of these represents a truly distinct disease entity or just a variation within a larger group.

This article summarizes the evidence base that was identified by this subcommittee as specifically pertaining to lung adenocarcinoma presenting as multiple nodules with GG/L features. This effort focused primarily on data pertaining to patients with multiple sites of such disease

and does not constitute a comprehensive review of solitary subsolid or lepidic lung cancer; for the latter we refer to other recent reviews.[9,11,18–20] This article also addresses lung cancers with diffuse pulmonary involvement, often called pneumonic adenocarcinoma. This entity typically presents radiologically with varying areas of ground glass and consolidation, although the appearance is more regional and patchy than nodular. Microscopically, these tumors are typically invasive mucinous adenocarcinomas with a predominance of lepidic growth. However, although there are features of the appearance of pneumonic adenocarcinoma that have similarities to multifocal lung cancer with prominent GG/L features, many aspects of the behavior of these entities are different.

The evidence base was used to formulate criteria to identify these entities for the purpose of providing guidance for consistent categorization. Taking into account the particular issues presented by these entities, we provide guidance on how to apply the TNM classification to these tumors to facilitate consistent classification and address the sources of confusion associated with lung cancer involving multiple pulmonary sites of malignancy.

## Methods

The IASLC database[21] was not informative for this topic because data on ground glass or lepidic features of lung cancers or on pneumonic-type adenocarcinoma were not captured. To develop an evidence base, the multiple nodules subcommittee conducted a systematic review with a methodologist's help for relevant literature from 1995 to 2015, building on a prior systematic review of patients with multiple tumor lesions that was conducted by the American College of Chest Physicians (ACCP) for the Lung Cancer Guidelines (third edition).[22] Reference lists of identified articles were also examined, and each article in the American College of Chest Physicians guideline was revisited to ensure correct data abstraction pertaining to the patients relevant to this review. The population, intervention, comparator, and outcomes questions, as well as the search structure, inclusion and exclusion criteria, and results, are available on request.

The identified evidence was reviewed and interpreted; an iterative process was used to develop a structure to identify homogeneous cohorts of tumors and propose how the TNM classification rules should be applied to these cohorts. Successive drafts were discussed and circulated to the entire subcommittee for revision. The article was then sent for critical review to an extended workgroup of individuals with particular interest and expertise in this topic (see the Appendix), as well as further review and eventual endorsement by the entire SPFC.

## Results: Multifocal Lung Cancer with GG/L Features

### *Evidence Base*

**Terms.** A ground glass nodule (GGN) is defined as a focal nodular area of increased lung attenuation on a CT scan through which normal parenchymal structures (i.e., airways and vessels) can be visualized (see Table 1 for a glossary of terms). A GGN is purely ground glass; nodules with a solid component are referred to as part-solid lesions. The term *subsolid* includes both pure ground glass and part-solid nodules.

**Table 1.** Glossary of Terms

| Term | Definition |
|---|---|
| Ground glass nodule (GGN) | Focal nodular area of increased lung attenuation on a computed tomography scan through which normal parenchymal structures (i.e., airways and vessels) can be visualized. These are pure ground glass, with no solid component |
| Part-solid nodule | A discrete lung parenchymal nodule with both a ground glass and a solid component |
| Subsolid nodule | A discrete lung parenchymal nodule that can be either pure ground glass or part solid |
| Multifocal ground glass/lepidic (GG/L) lung adenocarcinoma | Multiple discrete nodules of lung cancer that have ground glass features (either pure or part solid) on imaging or lepidic features on histologic examination (with or without an invasive component) |
| Atypical adenomatous hyperplasia (AAH) | Small (usually $\leq$5 mm) localized proliferation of mildly to moderately atypical cells lining the alveolar walls |
| Adenocarcinoma in situ (AIS) | Small ($\leq$3 cm) adenocarcinoma with growth restricted to neoplastic cells along preexisting alveolar structures and lacking stromal, vascular, or pleural invasion |
| Minimally invasive adenocarcinoma (MIA) | Small ($\leq$3 cm) adenocarcinoma with a predominantly lepidic pattern and $\leq$5 mm invasion in the largest dimension |
| Lepidic predominant adenocarcinoma (LPA) | Bland pneumocystic cells growing along alveolar walls, with an invasive component >5 mm |
| Pneumonic-type lung adenocarcinoma | Pneumonia-like area of infiltrate/consolidation involving a region of the lung. Histologically, this is usually predominant lepidic growth, with partial filling of alveolar air spaces by mucin or tumor cells |

The pathologic correlates of this radiographic appearance are adenocarcinoma subtypes, primarily lepidic-predominant adenocarcinoma (LPA), minimally invasive adenocarcinoma (MIA), adenocarcinoma in situ (AIS), or atypical adenomatous hyperplasia (AAH), all of which have a predominant lepidic component (Table 1).[9] Lepidic refers to a growth pattern whereby atypical pneumocytes proliferate along alveolar walls (think of a butterfly [Order Lepidoptera] alighting on a branch but not disturbing it).

A term encompassing both the radiographic and histologic features of these cancers is needed to denote this pattern of disease. The term *GG/L* addresses this and includes both pure ground glass and part-solid nodules (radiographic appearance) and lepidic adenocarcinomas with or without an invasive component (histologic features).

**Descriptive Characteristics.** Numerous studies have consistently reported that multifocal GG/L lung adenocarcinomas occur mostly (60%–80%) in women, which is in contrast to non–small cell lung cancer (NSCLC) in general.[12,23–29] This observation is made in both Asian and North American populations. The proportion of nonsmokers (30%–80%) varies with the regional prevalence of smoking but is always greater than the general prevalence in patients with lung cancer in that region. These findings suggest a potentially different etiology for multifocal GG/L lung cancers.

There is a general correlation between the radiographic (CT) appearance and histologic findings, but it is imperfect. Among multifocal tumors with a pure ground glass appearance, some (14%–80%) were found to be invasive adenocarcinoma.[28–30] Of those that were more than 50% ground glass, some (0%–85%) were reported to be pure BAC (according to the 2004 WHO definition) and some (15%–100%) were reported as adenocarcinoma with BAC features.[29–31] The tumors in these reports would probably be variously classified as AIS, MIA, or LPA if the current WHO classification were used.[32] Advances in image quality and histologic definitions do not appear to adequately account for the variability. Studies involving primarily solitary subsolid nodules note that lesions are reported as adenocarcinoma (with BAC features) in approximately 10% (7%–30%) of pure GGNs and approximately 50% (15%–80%) of part-solid (>50% ground glass) lesions.[11,23,31,33–42] Thus, although there is a general trend, radiographic findings do not correlate well with the histologic diagnosis. To an extent, this suboptimal correlation may reflect ambiguities in the histologic terms (i.e., BAC), or interobserver variability in the radiographic characterization of nodules.[43]

**Histologic and Molecular Characteristics.** Although GG/L tumors are all adenocarcinomas, there are often differences between lesions with respect to proportions of adenocarcinoma subtypes. We surmise that many of these lesions could be considered separate primary tumors by a comprehensive histologic assessment.[44] However, this has never been studied, and there may be a sizable proportion of lesions that appear similar.

Although intraobserver variability is low ($\kappa$ = 0.78-0.87),[45] some interobserver variability exists among dedicated thoracic pathologists in identifying the predominant subtype among lung adenocarcinomas in general (not specifically GG/L lesions).[45–47] In a study involving 100 consecutive adenocarcinoma cases and five dedicated thoracic pathologists, agreement on the predominant pattern was achieved in 66% of cases ($\kappa$ = 0.44–0.62).[45] In a study involving the evaluation of 19 *typical* cases for each of five adenocarcinoma subtypes by 26 thoracic pathologists, the predominant pattern was consistently identified in 92% to 100% of cases (except micropapillary with consensus in 62%).[47] On the other hand, in a study involving 40 *difficult* cases and 51 thoracic pathologists, consensus on the predominant subtype of adenocarcinoma was achieved initially in 51% to 74% of cases (lepidic 57%, papillary 63%, acinar 51%, micropapillary 64%, and solid 73%).[46] Training improved these results somewhat (consensus in 60%–75%).[46] There is also interobserver variability in identifying the presence of invasion.[47] In a study involving 28 thoracic pathologists who evaluated 64 typical and difficult cases for the presence of invasion, complete agreement was seen in 10% of cases, and less than 10% discordance in 29% (on a 3-point scale: probable and definite invasion, unclear, and probably or definitely not invaded; $\kappa$ = 0.55 for typical cases and 0.15 for difficult cases).[47] How this interobserver variability between cases might affect consistency of classifying invasion or the predominant subtype among different lesions in a patient with multiple GG/L tumors is unclear and has not been studied.

Multifocal adenocarcinomas with lepidic features may be nonmucinous, mucinous, or mixed. Among studies reporting on GG/L tumors, approximately 50% (38%–64%) are nonmucinous, approximately 35% (22%–52%) mucinous, and approximately 15% (3%–18%) mixed.[27,48–50]

Clonality studies comparing these multiple lesions in a single patient are limited and conflicting. Recent studies suggest that most of these are separate primary cancers; in those patients with multifocal GG/L lung cancer in whom clonality could be assessed, 71% to 83% were discordant,[51–53] However, earlier smaller studies suggested either the same[54,55] or separate lineage[56] for all lesions.

**Biologic Behavior.** An understanding of the innate biologic behavior of a cancer is provided by natural history studies (outcomes in the absence of any treatment

intervention); an approximation of this can be gained from studies in which multifocal subsolid lung cancers were observed for a time. In three studies specifically addressing multifocal GG/L lung cancer, 60% to 95% of pure GGNs remained stable, a few decreased or disappeared, and a few increased or became part solid (prompting resection).[57–59] These studies involved 28, 23, and 23 patients (40, 89, and 196 nodules), with median observation periods of 24, 40, and 49 months, respectively.[57–59] This is consistent with a recent review[11] involving mostly studies of solitary subsolid nodules, in which most nodules remained stable, approximately 20% decreased or disappeared, and 20% increased or became more solid (involving median observation periods of 9–50 months). The proportion that grew or became more solid was somewhat higher among part-solid nodules than among pure GGNs.

Outcomes after resection of multifocal GG/L lung adenocarcinoma have been reported to be excellent (~90% 5-year overall survival [OS], Table 2). The studies listed have predominantly involved patients with multiple nodules that were largely part solid. Despite this, the incidence of N2 node involvement has been low. This is consistent with other data indicating that GG/L lung adenocarcinomas in general exhibit more indolent behavior.[11,27,61,62] The risk of invasive cancer does not differ whether there is a single subsolid nodule or multiple subsolid nodules.[23,28,35,57,58,63] On the other hand, data from the Surveillance, Epidemiology, and End Results registry from 1998 to 2002 involving patients coded as having multiple "BAC" lesions show mediocre outcomes (Table 2): a 48% 5-year OS for same-lobe multiple lesions (mostly resected) versus a 7% to 25% 5-year OS when different lobes were involved (but only 21% were resected).[27] We have little additional information about these patients (e.g., CT characteristics), and we must recognize the ambiguity of a diagnosis of BAC from this period.

The pattern of recurrence of multifocal GG/L lung adenocarcinoma is shown in Table 3. Distant recurrence is distinctly unusual. Local recurrence and the appearance of new primary lung lesions are predominant; how a new pulmonary lesion is classified may account for some variability among these. Other studies involving mostly solitary GG/L lung cancers have also reported a decreased propensity for nodal or systemic spread and a markedly increased propensity for the development of additional pulmonary foci compared with in NSCLC in general.[20,24,48,62,64–72]

## Criteria Identifying Multifocal GG/L Tumors

It is important to define criteria by which we can recognize particular patterns of disease. The multiple nodules subcommittee developed the criteria shown in Table 4 for GG/L lesions. The rationale for these criteria is as follows. Recognizing this pattern of disease (multiple GG/L lesions) addresses a commonly encountered group of patients. There is a substantial body of evidence

**Table 2.** Multifocal Ground Glass/Lepidic Lung Adenocarcinoma

| First Author | No. Patients | % pN2 | % Resected | Location | % Multifocal | CT Appearance (% Ground Glass) | | | % BAC[a] Histotype | | % 5-Year Survival | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | <50% | >50% | Pure | Mixed | Pure | All | pN0 |
| Ishikawa[25] | 93 | 8 | 100 | Various | 87 | 26 | 51 | 22 | – | – | 87 | 93 |
| Vazquez[30,b] | 49 | 10[c] | 100 | Various | 100 | 42 | 23 | 34 | 74 | 12 | – | 100 |
| Nakata[29] | 31 | 6 | 100 | Various | 84 | 28 | 43 | 29 | 69[d] | 31 | 93 | – |
| Ebright[12] | 29[e] | 3[c] | 100 | Various | 100 | – | – | – | 66 | 34 | 68 | – |
| Mun[28,b] | 27 | 0 | 100 | Various | 93 | 0 | – | – | 14 | 86 | 100[f] | 100[f] |
| Kim[58] | 23 | 0 | 100 | – | 100 | 0 | 0 | 100 | 0 | 69 | 100 | 100 |
| Roberts[60] | 14 | 0 | 100 | Various | 100 | – | – | – | 14 | 57 | 64 | 64 |
| **Average** | | | | | | | | | | | **85** | **91** |
| Registry data | | | | | | | | | | | | |
| Zell 2006[27] | 93 | 11 | 91 | Same L | 100 | – | – | – | – | – | 48[f] | – |
| Zell 2006[27] | 80 | 22[g] | 68 | Ipsi DL | 100 | – | – | – | – | – | 25[f] | – |
| Zell 2006[27] | 198 | 22[g] | 21 | Bilat L | 100 | – | – | – | – | – | 7[f] | – |

*Note:* Inclusion criteria: studies involving multifocal lung adenocarcinoma and at least 10 patients from December 1995 to April 2015.
[a]Although the term *bronchioloalveolar carcinoma* has been abandoned, it was in use at the time these papers were written.
[b]Involving primarily patients detected by CT screening for lung cancer.
[c]N1 and N2 combined.
[d]Includes adenocarcinoma.
[e]Patients with pneumonic (infiltrative) adenocarcinoma excluded.
[f]Four-year overall survival.
[g]Both ipsilateral and bilateral different lobes reported together.
BAC, bronchioloalveolar carcinoma; Bilat L, bilateral lobes; CT, computed tomography; Ipsi DL, ipsilateral different lobe; L, lobe.

**Table 3.** Recurrence Pattern of Multifocal Ground Glass/Lepidic Lung Adenocarcinoma

| First Author | No. Patients | Type | Recurrence Type (%) New 1° | Lung | N2,3 | L + D | D |
|---|---|---|---|---|---|---|---|
| Ebright[12,a] | 47 | Pure GG | 43 | 38 | | 10 | 10 |
| Mun[28,b] | 27 | Pure GG | 100 | 0 | | 0 | 0 |
| Ebright[12,a] | 21 | >50% GG | 50 | 30 | | 10 | 10 |
| Ebright[12,a] | 32 | <50% GG | 62 | 23 | | 0 | 15 |
| Ishikawa[25] | 93 | Multifocal | —[c] | (53)[c] | (29)[c] | — | (18)[c] |
| Regnard[49,a] | 61 | BAC[d] | —[c] | (55)[c] | (15)[c] | — | (30)[c] |
| **Average**[e] | | | **64** | **23** | | **5** | **6** |

*Note:* Inclusion criteria: studies reporting recurrence patterns in multifocal lung adenocarcinoma and at least 10 patients from December 1995 to April 2015.
[a]Included patients with unifocal disease.
[b]Involving primarily patients detected by CT screening for lung cancer.
[c]Data for new primary cancers not reported.
[d]Pre-1999 definition.
[e]Excluding values in parentheses.
BAC, bronchioloalveolar carcinoma; CT, computed tomography; D, distant; GG, ground glass; L, local (intrathoracic).

that this pattern of disease is associated with good outcomes and infrequent nodal or extrathoracic recurrences (i.e., a biologic behavior different from that of the more typical NSCLC presenting as a solitary, solid spiculated mass). Criteria for this pattern of disease must take into account the clinical presentation because typically there are multiple foci, many of which are followed by serial imaging and not resected. Requiring a histologic characterization of each for pathologic classification would leave a large group (likely the majority) of such patients without a definition of how to classify them pathologically.

The pattern of GG/L nodules is essentially seen only with lung adenocarcinoma, so inherently there is some similarity between the lesions. Provided that there are multiple tumors with a prominent GG or lepidic component, categorization as multifocal GG/L tumors is appropriate; focusing on further differentiation among multiple GG/L tumors whether they have matching or only similar features on histologic examination is problematic for several reasons. We have no evidence that this is associated with a different behavior or outcomes. In such a setting, we have limited data about how well or consistently this can be done. Because there are often many lesions, there may often be a mixture of quite similar and less similar lesions, making categorization based on this histologic criterion complicated. Finally, a detailed histologic assessment approach is applicable only to resected lesions and is problematic in its application to actual patients (who frequently have lesions that are simply followed). Therefore we propose that tumors be included under the rubric of multiple GG/L tumors whenever there are multiple nodules with ground glass or lepidic features (which inherently implies some similarity), regardless of finer nuances of histologic similarity among them.

GG/L tumors have a prominent proportion of GG or lepidic growth. Foci of AAH, however, are not counted; the multifocal GG/L category applies to multiple tumors that are AIS, MIA, or LPA with or without other subtypes of adenocarcinoma, provided that there is a prominent lepidic component. Furthermore, there should be multiple tumors with a prominent proportion of GG or lepidic growth.

Although there is a spectrum of ground glass versus solid or lepidic versus invasive components, the categorization of GG/L tumor should not be used for tumors that are completely or almost completely (i.e., ≥90%) solid or invasive. Stated differently, a solid (spiculated)

**Table 4.** Criteria Identifying Multifocal Ground Glass/Lepidic Lung 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 found by biopsy 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 <5 mm 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 of adenocarcinoma denote different things.
AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; GGN, ground glass nodule; LPA, lepidic-predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma.

lung cancer should not be categorized as a GG/L tumor simply because a small amount of lepidic growth is seen at the periphery. Furthermore, minute separate foci of neoplastic growth are not counted, in recognition of the fact that on careful review, a background of such lesions can often be found in the resected lung. A solid/invasive lung cancer should not be classified as a multifocal GG/L tumor because such small lesions are detected.

A patient with a solid or almost completely solid tumor and (an)other prominently GG or lepidic tumor(s) should be categorized as having separate primary tumors; indeed, the histologic appearance would be different.

### *Proposal for the Application of TNM Classification to Multifocal GG/L Tumors*

Multifocal GG/L lung adenocarcinoma should be classified by the T category of the lesion with the highest T, with the number of lesions or simply *m* for multiple indicated in parentheses, and an N and M category that applies to all the multiple tumor foci collectively—for example, T1a(4) N0 M0. According to new proposals described elsewhere,[73] the size is determined by the largest diameter of the solid component (by CT) or the invasive component (under the microscope). The designation of Tis should be used for AIS and T1a(mi) for MIA —for example, T1a(mi)(m) N0 M0.

All of the parenchymal tumors in both lungs are collectively captured by the T component—that is, T(#/m) regardless of location (e.g., same lobe, different lobe, or lung). The T component should include all tumors whether resected or not that are thought to be malignant (either suspected or proved). Furthermore, the T(#/m) multifocal classification should be applied to both grossly recognizable tumors and those that are discovered only on pathological examination (microscopically or otherwise).

**Rationale.** The T(#/m) designation has been a longstanding part of the Union for International Cancer Control and the American Joint Committee on Cancer general rules for TNM classification, specifically for "multiple synchronous primary tumors of one organ."[74,75] The multiple GG/L pattern of disease appears to be what this T(#/m) designation was intended for. The single T category for all pulmonary lesions together (including noting the T category of the lesion with the highest T) seems to be both practical and appropriate. It appears to be reflective of the prognostic impact of the tumor extent (i.e., the highest T lesion). Typically there are multiple lesions; sometimes counting an exact number can be difficult for the pathologist or radiologist and influenced by technical aspects of imaging. The T(m) designation remains easy to apply in such situations. The 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.

**Practical Concerns.** We suggest that pure GGNs smaller than 5 mm not be taken into account. Thinner slices (e.g., 1.25 mm) and other technologic advances are desirable, as they provide greater sensitivity to detect faint GGNs or small solid areas.[76] We also suggest that tumors that are almost completely solid or invasive (i.e., have a ground glass or lepidic component of $<10\%$) not be classified under this rubric; such tumors should be classified separately from tumors that have a significant ground glass/lepidic component. We recognize that these practical suggestions are arbitrary and not evidence based. Hence they should be viewed as suggestions and not as rules. Judgment is needed, especially for tumors that are near the boundaries that are inherent to any classification system.

**Progression/Recurrence.** New GG/L tumor(s) that develop in a patient with a previous (resected) multifocal GG/L adenocarcinoma should be classified as a new second primary cancer if no lesion was previously present at the site of the new GG/L tumor. Lesions that were previously simply observed but subsequently progress enough to warrant intervention should be designated by the current size and other characteristics of the lesion at the present time; stage classification is always linked to the time of assessment. For example, at the time of resection of a GG/L tumor(s), additional lesions may be noted but managed conservatively by observation (e.g., a pure GGN). If such lesion(s) subsequently progress (perhaps warranting resection), they should be designated by their characteristics at the current time—for example, T1a(#/m) N0 M0. The fact that they were noted previously has no impact on the current TNM classification. A designation of recurrent disease is applicable only if there is clear evidence of recurrence of exactly the same tumor after a disease-free interval.[74,75]

## Results: Pneumonic-Type Lung Cancer

### *Evidence Base*

Some patients exhibit a diffuse pattern of lung cancer that is similar radiologically to a pneumonia (hence the name "pneumonic-type lung cancer").[48,49,66,77,78] This form of adenocarcinoma has some similarities to but also many differences from multifocal GG/L adenocarcinoma. It is unclear whether this represents an extreme form of multifocal adenocarcinoma, a later stage in the evolution of this entity, or a different entity altogether.

Garfield et al.[79] reviewed the literature in 2008 and argued that mucinous and nonmucinous BAC are

separate entities. This was based on a different putative cell of origin and differences between mucinous and nonmucinous BAC by immunohistochemical analysis (cytokeratin 20 in 53% versus in 3%; thyroid transcription factor 1 in 24% versus in 88%) and biomarkers (*EGFR* mutations in 3% versus 45%; *Kras* viral oncogene homolog in 34% versus 14%, respectively).[79]

It is thought that most pneumonic-type adenocarcinomas are invasive mucinous adenocarcinomas, particularly with the 2015 WHO classification.[32] In the existing literature there is moderate correlation between imaging and histologic subtype (Table 5). Among mucinous tumors a consolidative pattern was noted in 33% to 75%,[49,70,81,82] and 75% had areas of ground glass.[81] In addition, several studies reported no significant differences between mucinous and nonmucinous tumors in terms of the proportion with a nodular versus a pneumonic presentation.[49,70,80,82] Conversely, among the larger historical studies reporting specifically on pneumonic-type lung cancer, approximately 45% (26%–57%) were mucinous, approximately 40% (29%–53%) nonmucinous, and approximately 15% (12%–21%) mixed (mucinous and nonmucinous) adenocarcinoma.[49,70,77]

**Descriptive Characteristics.** The demographic data are limited; the mean age of patients with pneumonic-type lung adenocarcinoma has varied from 41 to 66 years, and the sex distribution is reported as either a preponderance of women or men, perhaps reflecting differences in definitions of terms or by geographic region.[77,83] Others have reported no difference in age, sex, or smoking status for pneumonic-type adenocarcinoma compared with for other forms of BAC.[33]

In the largest series (n = 52) of pneumonic-type adenocarcinoma consolidation was seen in 83%; in 63% there were additional areas of involvement in another lobe and bilateral disease in 58%.[77] This study involved surgical and nonsurgical patients. In other series involving surgical patients the proportion of bilateral disease is lower.[70]

**Histologic and Molecular Characteristics.** Under the microscope it appears that pneumonic-type adenocarcinoma typically has a homogenous appearance throughout, especially when the mucinous form is involved. However, this has not been formally studied or quantified, and it is less clear whether the nonmucinous or mixed forms are homogeneous or heterogeneous.

Limited investigation of clonality in pneumonic-type adenocarcinoma has been carried out. A study of a patient with pneumonic-type adenocarcinoma found evidence of different clonality in each of five lobes.[84] This involved immunohistochemical analysis (carbohydrate antigen 19-9, carcinoembryonic antigen, and *p53* protein), polymerase chain reaction, and fluorescence-based single-strand conformation polymorphism and sequencing after cloning to compare *p53* point mutations and specific DNA base pair substitutions.

**Biologic Behavior.** Patients with pneumonic-type adenocarcinoma typically present without nodal or systemic metastases despite diffuse pulmonary involvement (Table 5); the occasional use of double-lung transplantation as a treatment underscores this.[62,85,86] The observation that recurrence (which occurred in more than half of cases) was almost always confined to the (transplanted) lung[85–88] is further evidence of both the unusual pulmotrophic nature of this entity and our limited understanding of the process of metastasis and the microenvironment.

Data on outcomes after curative treatment are limited, presumably owing to the diffuse nature; survival after resection is clearly worse than in patients with multiple distinct foci of GG/L cancers. Recurrences occur primarily in the remaining lung (Table 5).

**Diffuse Miliary Adenocarcinoma.** There are also patients who are found to have diffuse "miliary" foci of

**Table 5.** Pneumonic-Type Adenocarcinoma

| First Author | No. Patients | Presentation, % | | | | Histologic Type, % | | | % 5-Year Overall Survival | | | Recurrence Type, % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Bilateral | N2,3 | M1b | Resected | Mucinous | Mixed | Nonmucinous | All | Resected | pN0 | L | L + D | D |
| Wislez[77] | 52 | 58 | 22 | 6 | 38 | 26 | 21 | 53 | 13 | 36 | – | 93 | – | 7 |
| Okubo[70] | 25 | 40 | – | – | 56 | 44 | 12 | 44 | – | 40 | – | – | – | – |
| Regnard[49] | 21 | – | – | – | – | 57 | 14 | 29 | – | 27 | – | 80 | – | 20 |
| Dumont[80] | 12 | – | 33 | 0 | 100 | 50 | – | 50 | – | 25 | – | – | – | – |
| Ebright[12] | 7 | – | 0 | 0 | 100 | 100 | 0 | 0 | – | 27 | 27 | 80 | 0 | 20 |
| Casali[48] | 7 | – | – | 0 | 100 | 86 | 0 | 14 | – | 28 | – | – | – | – |
| **Average** | | | | | | | | | | **31** | | **84** | **–** | **16** |

*Note:* Inclusion criteria: studies reporting specifically on pneumonic-type adenocarcinoma in at least 5 patients from December 1995 to April 2015.
D, distant; L, local (intrathoracic).

adenocarcinoma, sometimes noted only on histologic examination of lungs that appeared radiologically normal. Such patients have not been specifically studied enough to allow characterization of demographics, risk factors, or biologic behavior, but it is implied that they are similar to other patients with multifocal or pneumonic-type lung cancer.[20,71]

## *Criteria Identifying Pneumonic-Type Lung Cancer*

The multiple nodules subcommittee developed the criteria shown in Table 6 for pneumonic-type adenocarcinoma with the following rationale. The diffuse consolidative, regional involvement is distinct from that of multiple GG/L nodules or the solitary mass of the typical primary NSCLC. The biologic behavior of this pattern of disease is also distinct, with a worse prognosis than that of multiple GG/L nodules, yet infrequent nodal or extrathoracic involvement.

## *Proposals for the Application of TNM Classification to Pneumonic-Type Adenocarcinoma*

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, N and M determined by nodal or extrathoracic involvement).[89,90] 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). 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 or M1b designation. The classification should be applied to both grossly recognizable lesions and those that are only discovered on pathological examination (microscopically or otherwise). This classification scheme should be used for pneumonic-type adenocarcinoma regardless of whether it is mucinous, nonmucinous, or mixed. Furthermore, although it is generally the case that different areas of pneumonic-type adenocarcinoma are histologically similar, the classification scheme should be applied without requiring a detailed histologic assessment to determine whether multiple details are exactly matching.

Particularly with the diffuse nature of pneumonic-type adenocarcinoma, it can be difficult sometimes to define discrete boundaries. 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.

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.

**Rationale.** The pneumonic type of adenocarcinoma generally has a similar histologic appearance throughout. Therefore, there is a parallel to applying TNM

**Table 6.** Criteria Identifying the Pneumonic Type of Adenocarcinoma

| |
|---|
| **Clinical criteria** |
| Tumors should be considered pneumonic-type of adenocarcinoma if |
| The cancer is manifested 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 should involve a regional pattern of distribution. |
| • The involved areas may appear to 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 of 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.

classification as is done for separate tumor nodules. A designation by the location of lobes that are involved seems practical for a diffuse disease in which measurement of size may be difficult. Furthermore, it stands to reason that the lobar extent of involvement may have prognostic value, although this has not been specifically reported. The decreased propensity for nodal and extrathoracic metastases supports the concept of a single N and M for the entire pulmonary areas of involvement.

A T category for multiple areas of pulmonary involvement also seems appropriate for miliary forms of adenocarcinoma. Although few data are available, the difficulty of linking an N or M site of involvement to a particular primary tumor site and the diffuse nature of the primary tumor involvement makes this appealing.

## Discussion

We have structured our approach according to patterns of disease. Whether each of these represents a truly distinct disease entity or just a variation within a larger group can be debated. However, this is also a matter of semantics—for example, is lung cancer one entity and squamous carcinoma and adenocarcinoma (or acinar predominant, LPA, etc.) simply variations, or should we view these each as separate entities?

A review of available information on lung cancers presenting as multiple nodules with GG/L features reveals several distinctive characteristics. These tumors occur more frequently in women and nonsmokers, suggesting the influence of different etiologic factors compared with in NSCLC in general. The rate of progression seems to be more indolent. There appears to be a decreased propensity for nodal and distant metastases but an increased propensity for the development of new pulmonary lesions. After resection, the long-term outcomes are very good, better than those of NSCLC with separate solid tumor nodules or solid second primary NSCLCs.[15–17] The fairly high incidence of patients with multiple GG/L tumors and the multiplicity of such nodules stand in contrast to the infrequent incidence of patients with solid second primary lung cancers (rarely $>2$), suggesting that these are different entities. Finally, multifocal GG/L adenocarcinomas are relatively easily recognized both clinically and by histologic examination. These factors led the multiple nodules subcommittee of the IASLC SPFC to specifically recognize this entity. The proposed criteria should help promote consistent reporting and future research to better understand the nature of these tumors.

Several characteristics of multifocal GG/L lung adenocarcinomas suggest that TNM classification is best done by using a method that has long been in existence in the American Joint Committee on Cancer/Union for International Cancer Control manuals for multiple tumors in one organ, with the highest T lesion defining the T category and the multiplicity of the tumors represented in parentheses—for example, T1a(4) or T1a(m)—and a single N and M assigned for all tumors together. These multifocal GG/L lung cancers are adenocarcinomas with a low incidence of nodal and distant metastases. They often consist of many lesions, making separate TNM staging of each one unwieldy.

Clinical utility is of major importance, meaning the ability to use this in daily practice for both clinical and pathologic staging. The T(#/m) classification is applicable not only before resection but also after resection by accounting for additional subsolid nodules without necessitating resection and pathologic characterization of all lesions. This is particularly important for these patients, as it is not uncommon to resect one lesion but continue to observe others.

A binary view of separate versus related tumors may be too rigid. The frequent multiplicity of GG/L tumors suggests the presence of a common etiologic factor or factors; the frequent observation of patients with lesions of different sizes and proportions of solid components suggests that at least some steps in the process of malignant transformation occur independently. Thus, GG/L tumors may have similarities as well as differences. The degree of similarity versus difference may best be viewed as gradations along a continuum. This supports a classification schema that avoids necessitating a detailed comparison of each lesion and a potentially difficult-to-define boundary characterized by subtle findings.

We recognize that additional clinical information may not be automatically apparent to the pathologist. However, a fundamental rule of TNM classification is that pathologic classification be "based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathologic examination."[74,75] When a prominent lepidic component to an adenocarcinoma is present, and especially when there are multiple such lesions, the presence of a multifocal GG/L lung adenocarcinoma should be suspected; the tumors should be categorized as such if consistent with the entirety of the information pertaining to that patient.

The relationship of diffuse pneumonic-type adenocarcinoma to multifocal GG/L adenocarcinoma is not clear. These may be different entities or just different parts of the spectrum of the same entity. Although the pneumonic form is mostly associated with mucinous (versus nonmucinous) histologic findings, there is some overlap; distinguishing GG/L from pneumonic-type cancers solely on the basis of histologic subtype is not ideal. We suggest that patients with diffuse versus multifocal nodular forms of adenocarcinoma be reported separately to clarify the relationship.

The diffuse pneumonic-type adenocarcinoma is traditionally thought of as a single cancer with diffuse involvement. Therefore classification of this pattern of disease as a single T (or M1a if bilateral) is in keeping with this tradition. The decreased propensity for nodal or distant metastases supports using a single N and M for these tumors.

Many questions regarding multifocal GG/L lung adenocarcinoma are unanswerable. Are these tumors really a different type of lung cancer, or do they simply appear different because they are observed in a different phase of development? In other words, do GG/L cancers eventually become "typical" solid, spiculated adenocarcinomas? Are they really inherently more indolent, or does the rate of growth and propensity for metastasis change over time? The fact that patients with subsolid nodules typically have many nodules whereas patients with separate solid tumor nodules usually only have one or two (and no additional GGNs) suggests that these are different entities. Similarly, diffuse (pneumonic or miliary) disease without the development of nodal or distant metastases appears to be a different entity than the typical solid spiculated lung cancer with frequent nodal and distant metastases. But the true nature of these forms of lung cancer and their relationship to one another is unclear.

It is important to emphasize that the TNM classification is intended primarily to provide a nomenclature for the anatomic extent of disease. How a patient should be managed is a different matter from how the tumor should be classified. Furthermore, the anatomic extent of disease is only one factor affecting prognosis; other factors include the type of cancer, the treatment given and the effectiveness thereof, patient-related factors, and structural factors (e.g., the health care system). TNM classification is only a tool to facilitate discussion of treatment strategy and prognosis.

Being able to consistently define a cohort of patients is a prerequisite to conducting and reporting investigations. Patients with multiple malignant pulmonary lesions have presented a particular challenge because of lack of distinction between disease entities with markedly different biologic behavior as well as confusion about how to apply TNM classification rules. We hope that the definitions proposed here pave the way for research that will answer the many open questions. We expect that further research will highlight aspects of the proposed definitions that need improvement. However, we believe that the currently available evidence justifies recognition of distinct patterns of disease. We believe that the proposed criteria and clarification of how to apply TNM classification to these tumors represent a step forward along the path toward both scientific progress and patient management.

## Conclusion

An increasing proportion of patients are presenting with multiple tumors that have a prominent ground glass component by imaging or lepidic component by microscopy. This creates difficulties in the assignment of TNM categories. It is proposed that the T category of such GG/L tumors be classified using the T category of the highest T lesion and in parentheses either the number of GG/L tumors or simply *m* for multiple. This classification scheme should be used regardless of nuances of similarities versus differences among the GG/L tumors, recognizing that by definition these will be similar. A single N and M category is assigned for all GG/L tumors combined (the incidence of nodal or extrathoracic involvement is unusual). Both clinical information (the presence of additional lesions identified by imaging) and the pathologic information (from resected lesions) should be used to determine the TNM classification. Lesions that are pure ground glass and smaller than 5 mm or AAH are not counted. The pneumonic type of adenocarcinoma should be classified according to the size of the area of lung involved, or as T4 or M1a in the case of involvement of more than one lobe (i.e., either ipsilateral or contralateral). A single N and M category is assigned. Consistency in nomenclature to describe these tumors will greatly facilitate the ability to develop a greater understanding of the nature of these entities, their behavior, and how such patients should be managed.

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## Appendix

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