Early-stage pulmonary adenocarcinoma (T1N0M0): a clinical, radiological, surgical, and pathological correlation of 104 cases. The MD Anderson Cancer Center Experience

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The recent proposal for histological subtyping of pulmonary adenocarcinoma by predominant pattern and introduction of the terms *adenocarcinoma in situ* and *minimally invasive adenocarcinoma* to replace the term *bronchioloalveolar carcinoma* by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society has led us to conduct a study of 104 patients with early-stage primary pulmonary adenocarcinoma (T1N0M0), with a view to histological subtype as defined by the new proposal and clinical outcome. None of the clinical parameters of our patient population (type of surgery, age, gender, tumor size, and comorbidities) showed any statistically significant correlation with outcome, except for associated malignancies, which not surprisingly appeared to have a negative impact on survival. In addition, statistical analyses of the histological characteristics to include tumor differentiation and the percentage of a lepidic or bronchioloalveolar component did not show any statistically significant values in terms of survival. Our results failed to show any statistically significant difference of survival between those T1N0M0 adenocarcinomas with a lepidic component and those without, thus questioning the use of terms such as *in situ* or *minimally invasive adenocarcinoma*. On the basis of our results, we consider that the outcome for patients with T1N0M0 disease is still best determined by appropriate staging rather than by changes in the pathology nomenclature of adenocarcinoma.

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Compared with other types of malignancies, lung cancer is the leading cause of death in the United States. According to the Surveillance Epidemiology and End Results (SEER) (<http://www.cdc.gov/cancer/lung/statistics/index.html> and http://seer.cancer.gov/csr/1975_2008/) in the year 2007, more than 203 thousand people were diagnosed with lung carcinoma, representing approximately 110 thousand men and 93 thousand women. The number of deaths due to lung cancer among this group was approximately 158 thousand. Also

according to SEER, the age group more commonly affected is individuals between the ages of 55 and 74 years, with a median age at diagnosis of 71 years. Although lung cancer is also seen in younger age groups, people under 45 years of age represent approximately 2% of the total number of cases, while those people between the ages of 45 and 54 years represent approximately 9% of the total number of cases. It is also suggested that factors such as smoking, dietary habits, family history, and chemical exposure to compounds such as asbestos, radon, and silica among many others may play a role in lung cancer pathogenesis. Of all the different types of lung cancer, adenocarcinoma is currently the most frequent.

In an effort to better define clinical behavior regarding small size adenocarcinomas, various studies have used different ways to address this issue.

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A recent publication endorsed by the World Health Organization (WHO)¹ has declared small adenocarcinomas with a pure lepidic growth pattern and absence of stromal, pleural, or vascular invasion as *bronchioloalveolar carcinoma*. In addition, more recently, in a study conducting a review of the current literature, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society² proposed that tumors up to 3.0 cm in greatest dimension with a pure lepidic growth pattern and lacking stromal, vascular, or pleural invasion should be categorized as *in situ adenocarcinoma*. Also, the same group designated a separate category of *minimally invasive adenocarcinoma* for tumors with a predominantly lepidic growth pattern and <5 mm invasion in greatest dimension in any one focus.

Following those parameters, we conducted a study of 104 patients diagnosed with early-stage adenocarcinoma (T1N0M0) of all histological types and found that when all these tumors are viewed as a group, there is no statistically significant correlation between histology and survival and that terms such as *in situ adenocarcinoma* or *minimally invasive adenocarcinoma* do not have any significant clinical impact. Thus, we still consider that staging is the most important parameter to predict prognosis. A detailed clinical, radiological, surgical, and pathological assessment of these tumors is herein presented.

Materials and methods

Materials

A search for tumors in the category of T1 adenocarcinoma of the lung was conducted from the files of the Departments of Pathology and Thoracic Surgery at MD Anderson Cancer Center (Houston, TX, USA) between the years 2005 and 2010. The following criteria were followed:

- Only patients with a diagnosis of primary adenocarcinoma of the lung who underwent surgical resection at MD Anderson Cancer Center were included in this study.
- All patients had to be properly clinically staged at the time of surgery.
- All radiological imaging films available had to be reviewed by the radiologists.
- All tumors had to measure at least 0.5 cm, but no more than 3 cm in greatest diameter.
- All surgical resections had to undergo pathological re-evaluation to verify not only the size of the tumor but also the histological growth pattern of the tumor.
- All available hematoxylin- and eosin-stained sections were evaluated; in those cases in which only a lepidic growth pattern was identified, the entire tumor was submitted for evaluation.

- The preoperative biopsy specimens of 66 cases were available for review and correlation with the resected material (in the remaining cases, either the diagnosis had been made on a cytology specimen or the original biopsy had already been returned to the original institution in which the initial biopsy had been taken; thus, that material was not available for re-examination).
- In cases in which the patients had another concurrent neoplasm, immunohistochemical studies, including TTF-1 (Dako, Carpinteria, CA, USA; 1:200), napsin A (Dako; 1:200), and cytokeratin 7 (Dako; 1:300), were performed obtaining positive results in all the cases diagnosed as primary lung adenocarcinomas. In addition, other stains including CDX2 (Biogenex, San Ramon, CA, USA; 1:50), S100 protein (CellMarque, Rocklin, MA, USA; 1:100), leukocyte common antibody (Dako; 1:50), keratin 20 (Dako; 1:100), gross cystic disease fluid protein (Abcam, Cambridge, MA, USA; 1:25), prostate-specific antigen (Dako; 1:200), and prostatic acid phosphatase (Dako; 1:200), mammoglobin (Dako; 1:100), renal cell carcinoma marker (Dako; 1:50), and Pax8 (ProteinTech Group, Chicago, IL, USA; 1:100) were also obtained depending on the patient's clinical history and pathological differential diagnosis, all of them with negative results.

On the basis of those parameters, a group of 248 cases was identified, which met the specified size criteria (0.5–3.0 cm). However, only 104 patients were finally selected in whom there was no evidence of lymph node and pleural involvement or metastatic disease (T1N0M0). In addition, patients with a prior history of lung carcinoma were excluded.

Methods

Clinical features. Demographic data were collected from our institutional computerized system about age, gender, presenting symptoms, comorbidities, associated malignancies, and type of surgical resection.

Radiology. Three chest radiologists (EMM, MFB, and MCG), who were blinded to the clinical outcome and the histopathological diagnosis of all cases, reviewed the preoperative chest CT scans and differences were resolved by consensus. Nodules were designated as: ground glass, defined as a hazy increased attenuation in the lung that does not obliterate the bronchial and vascular margins; solid, defined as homogeneous soft tissue attenuation; and part solid, defined as a nodule that consists of both ground glass and solid soft tissue attenuation components.

Pathology. Re-examination of all pathological material was conducted by three chest pathologists (AW, NK, and CAM). Histological re-evaluation of

the available preoperative biopsies ($n=66$) as well as the resection material ($n=104$) was performed. The percentage of a lepidic component was recorded for each of the biopsy specimens. The resected tumors were separated into the conventional categories of well, moderately and poorly differentiated adenocarcinoma based on tumor architecture, nuclear atypia, and mitotic activity. In addition, the tumors were further subdivided into categories based on the percentage of a lepidic growth pattern.

Statistical analysis. Association between clinical outcome and the following parameters was assessed: age, gender, comorbidities, associated malignancies, type of surgical treatment, tumor size, and tumor histology. Univariable and multivariable Cox proportional hazard regression statistical analyses were conducted using SSPS, version 17.0. All those covariates that had a P -value <0.25 in the univariable analysis were then entered into the multivariable analysis. Stepwise backward elimination using Wald's statistic was performed to obtain the final multivariable regression model. The log-rank test was performed when creating survival curves using the Kaplan–Meier method. Statistical significance was defined as a P -value ≤ 0.05 .

Results

Clinical Features

Among the patients used in this study, 65 were women and 39 were men between the ages of 49 and 86 years (mean 65 years). In all, 41 patients had one other associated malignancy and 7 patients had two or more associated malignancies, which included invasive melanoma ($n=9$), lymphoma/leukemia ($n=4$), prostatic carcinoma ($n=8$), breast carcinoma ($n=10$), renal cell carcinoma ($n=5$), endometrial carcinoma ($n=1$), esophageal carcinoma ($n=2$), soft tissue sarcoma ($n=2$), colonic carcinoma ($n=2$), gastric carcinoma ($n=1$), head and neck squamous cell carcinoma ($n=3$), Merkel cell carcinoma ($n=2$), urothelial cell carcinoma of the bladder ($n=1$), malignant salivary gland tumor ($n=1$), chordoma ($n=1$), and papillary thyroid carcinoma ($n=4$). In these patients, the finding of a pulmonary mass was detected during follow-up for their respective prior malignancy. In 56 patients, cough, dyspnea, and chest pain led to radiographic evaluation.

In addition, each one of the patients was also evaluated for comorbidities, which included cerebrovascular disease ($n=8$), diabetes mellitus ($n=3$), chronic alcohol use ($n=6$), arrhythmias ($n=5$), chronic obstructive pulmonary disease ($n=11$), cardiovascular disease ($n=5$), hypertension ($n=51$), as well as smoking history ($n=79$).

All patients underwent surgical resection of their tumors with respective proper surgical staging. In 91 patients, lobectomy was the treatment of choice, while in 13 patients a wedge resection or

Table 1 Univariable Cox regression for overall survival ($n=104$)

			95% CI for HR			
	Frequency	P-value	HR			
				Lower	Upper	
<hr/>						
<i>Type of surgery</i>						
Wedge/segmentectomy (Reference)	13					
Lobectomy	91	0.599	0.720	0.211	2.457	
<i>Tumor size</i>						
≤ 1 cm (Reference)	13	0.659	1.000			
> 1–2 cm	55	0.400	0.607	0.190	1.940	
> 2–3 cm	36	0.413	0.588	0.165	2.095	
Age at diagnosis	104	0.286	1.027	0.978	1.079	
<i>Gender</i>						
Female (Reference)	65		1.000			
Male	39	0.111	2.047	0.848	4.943	
Associated malignancies	48	0.049	2.521	1.004	6.328	
<i>Comorbidities</i>						
Cerebrovascular disease	8	0.537	0.530	0.071	3.974	
Diabetes	3	0.537	1.884	0.252	14.101	
Alcohol use (4 oz. a day)	6	0.370	1.957	0.451	8.491	
Arrhythmia	5	0.468	0.045	0.000	192.688	
Chronic obstructive pulmonary disease	11	0.104	2.489	0.829	7.476	
Coronary artery disease	5	0.816	1.270	0.170	9.497	
Hypertension	51	0.759	0.871	0.361	2.103	
Any tobacco history	79	0.703	1.238	0.413	3.707	
<i>Histological features</i>						
Tumor differentiation		0.105				
Well differentiated (Reference)	43		1.000			
Moderately differentiated	48	0.064	2.631	0.947	7.312	
Poorly differentiated	13	0.757	0.712	0.083	6.110	
<i>Lepidic Pattern</i>						
≤ 50% (Reference)	66		1.000			
> 50%;	38	0.121	0.419	0.140	1.257	

segmentectomy was performed. In all the cases, lymph nodes were dissected for appropriate staging. Statistical analysis of the types of procedure performed in these 104 patients demonstrated a lack of statistical significance ($P=0.599$) as to whether the patients were treated with lobectomy or wedge resection/segmentectomy (Table 1).

None of the clinical parameters studied with respect to outcome showed statistical significance, except for associated malignancies, which appeared to impact negatively on survival ($P=0.049$) (Table 1).

Radiological Features

Preoperative chest CT scans were available for review in 101 of the 104 study patients. In 49

Figure 1 (a) Low-power view of well-differentiated pulmonary adenocarcinoma with a lepidic growth pattern ('bronchioloalveolar carcinoma' and 'adenocarcinoma *in situ*'). (b) High-power view of well-differentiated adenocarcinoma ('bronchioloalveolar carcinoma' and 'adenocarcinoma *in situ*'). Neoplastic cells with mild atypia are lining the alveolar walls.

patients, the tumors were described as solid, 47 as partly solid, and 6 as pure ground-glass opacities.

Pathological Features

Retrospective analysis of the preoperative lung biopsy was possible in 66 cases, 24 of which showed a pure lepidic growth pattern. The biopsy specimens were also correlated with the surgical resection material of the tumors showing 19 cases with pure

lepidic growth pattern, while in 5 cases the resected specimens showed combined lepidic and non-lepidic growth patterns (including acinar, papillary, and solid patterns).

Grossly, the resected tumors were described as well-demarcated intrapulmonary masses of light tan to brown color and soft to firm consistency, ranging in size from 0.5 to 3.0 cm in greatest diameter. On the basis of these set criteria, 13 tumors were between 0.5 and 1.0 cm; 55 tumors between 1.1 and 2.0 cm; and 36 tumors between 2.1 and 3.0 cm.

The 104 tumors were initially analyzed using the conventional approach and using the architectural pattern of the glandular proliferation, nuclear atypia, and mitotic activity. On the basis of those parameters, the tumors were graded as:

- well differentiated, $n = 43$ (41%) (Figures 1a and b);
- moderately differentiated, $n = 48$ (46%) (Figure 2); and
- poorly differentiated, $n = 13$ (13%) (Figure 3).

Following this stratification of histological types, we encountered no statistical significance between tumor differentiation and outcome with a univariable P -value of 0.105 (Table 1). Further, multivariable analysis also showed no statistical significance with a P -value of 0.125 (Table 2).

In addition, the tumors were further analyzed and subdivided into two main categories: (1) those showing a lepidic or bronchioloalveolar growth pattern and (2) those with no histological evidence of a lepidic growth pattern. Histological evaluation of 104 cases disclosed that 59 cases showed evidence of a lepidic component, which was further divided into percentages:

- <25% lepidic component ($n = 10$);
- 25–50% lepidic component ($n = 11$);
- >50% lepidic component ($n = 38$).

or

- ≤50% lepidic component ($n = 21$);
- >50% lepidic component ($n = 38$).

In total, the number of cases showing 0 or ≤50% of a lepidic component corresponded to 66 cases, while those with more than 50% of a lepidic component represented 38 cases. Again, no statistical significance was encountered between tumors with ≤50% or >50% lepidic components and outcome with a univariable P -value of 0.121 (Table 1). Further, multivariable analysis also showed no statistical significance with a P -value of 0.834 (Table 2).

It is evident from Table 2 that even when the initial statistical cutoff P -value of <0.25 was lowered to 0.125, only tumor differentiation met the requirement for multivariable analysis as the percentage of a lepidic component did not converge into the final step, as this variable maintained a

Figure 2 Moderately differentiated pulmonary adenocarcinoma with recognizable glandular growth pattern and moderate cytologic atypia.

Figure 3 A more solid growth pattern and higher degree of cytologic atypia and mitotic activity is seen in this poorly differentiated pulmonary adenocarcinoma.

P-value of 0.834. Nevertheless, we still proceeded to analyze those tumors differently as presented below. Important to note is that none of the tumors herein presented fulfilled the criteria of 'minimally invasive adenocarcinoma' as per the new proposed classification.²

In view of the univariable statistically significant association between lung carcinoma and associated malignancies in relation to outcome ($P=0.049$), the

Table 2 Multivariable Cox regression for overall survival ($n=104$)

	Frequency	P-value	HR	95% CI for HR	
				Lower	Upper
<i>Initial step</i>					
<i>Gender</i>					
Female (Reference)	65		1.000		
Male	39	0.277	1.693	0.656	4.372
Associated malignancies	48	0.078	2.378	0.908	6.223
Chronic obstructive pulmonary disease	11	0.170	2.257	0.705	7.228
<i>Histological features</i>					
Tumor differentiation		0.125			
Well differentiated (Reference)	43		1.000		
Moderately differentiated	48	0.108	2.754	0.802	9.458
Poorly differentiated	13	0.715	0.652	0.066	6.458
<i>Lepidic Pattern</i>					
≤50% (Reference)	66		1.000		
>50%;	38	0.834	0.862	0.216	3.445
<i>Final step</i>					
Associated malignancies	48	0.028	2.832	1.122	7.151
Tumor differentiation		0.065			
Well differentiated (Reference)	43		1.000		
Moderately differentiated	48	0.034	3.035	1.085	8.488
Poorly differentiated	13	0.858	0.822	0.095	7.093

entire group of patients was further separated into two groups: (1) 48 patients in whom there was another associated malignancy and (2) 56 patients in whom there was not. The tumors of the latter group were then also subdivided into those with a lepidic component and those without. In this group, we identified 27 out of 56 cases with evidence of a lepidic component. The lepidic component was distributed as follows:

- <25% ($n=5$);
- 25–50% ($n=3$);
- >50% ($n=19$) (all the tumors in this group showed a pure (100%) lepidic pattern = so-called 'in situ adenocarcinoma');

or

- ≤50% ($n=8$);
- >50% ($n=19$) (all the tumors in this group showed a pure (100%) lepidic pattern = so-called 'in situ adenocarcinoma').

The total number of cases showing 0 or ≤50% of a lepidic component corresponded to 37 cases, while in 19 cases the tumors showed exclusively a lepidic pattern (the so-called 'in situ adenocarcinoma'). Statistical analysis of this subgroup of patients

Table 3 Univariable Cox regression for overall survival ($n = 56$)

	Frequency	P-value	HR	95% CI for HR	
				Lower	Upper
<i>Type of surgery</i>					
Wedge/segmentectomy (Reference)	7		1.000		
Lobectomy	49	0.928	0.906	0.109	7.534
<i>Tumor size</i>		0.974			
≤ 1 cm (Reference)	7		1.000		
> 1–2 cm	30	0.996	1.006	0.112	9.024
> 2–3 cm	19	0.879	0.830	0.075	9.185
Age at Diagnosis	56	0.443	1.032	0.953	1.117
Gender	17	0.457	1.766	0.394	7.911
<i>Comorbidities</i>					
Cerebrovascular disease	4	0.613	0.044	0.000	8006.615
Chronic obstructive pulmonary disease	6	0.073	4.533	0.870	23.610
Hypertension	31	0.448	0.560	0.125	2.503
<i>Histological features</i>					
<i>Lepidic pattern</i>					
≤ 50% (Reference)	37		1.000		
> 50%	19	0.262	0.025	0.000	15.954

showed no statistical significance between type of surgery (lobectomy vs wedge/segmentectomy), tumor size, age, gender, or comorbidities (Table 3). In addition, the presence of a pure lepidic pattern yielded a P -value of 0.262 (Table 3). Furthermore, we proceeded to perform Kaplan–Meier survival curves by comparing cases with no lepidic component against those with different proportions of a lepidic pattern. An initial trend towards better survival, although not statistically significant, was noted for cases with any lepidic component compared with those without ($P = 0.058$) (Figure 4a). However, when the tumors with lepidic component were separated by specific percentage, we did not encounter any statistical significance among the three groups (<25, 25–50, and >50%) ($P = 0.102$) (Figure 4b), nor when divided into two groups (≤50 and >50%) ($P = 0.118$) (Figure 4c), or even for tumors with pure lepidic pattern (the so-called ‘*in situ* adenocarcinoma’) ($P = 0.134$) (Figure 4d).

Follow-Up

Clinical follow-up was obtained in all patients (100%) with a median follow-up time of 48 months (range 1–82 months). A total of 20 patients died (19%) and 84 patients (81%) are alive without recurrence. Further analysis of the group of 56 patients in whom there was no other associated malignancy showed that the median follow-up was 57 months (11–82 months). In this group of patients, 7 patients died (13%) and 49 (87%) are alive with no

recurrence. In the patients who have died, we were not able to obtain further information regarding the exact cause of death. However, one of those patients had been followed for severe arrhythmias and hypertension. To the best of our knowledge none of these patients had recurrent disease. Comparison of these two patient groups showed a similar trend for cumulative survival (Figures 5 and 6). In addition, a comparative survival probability between patients with associated malignancies and those with no other malignancy is also presented (Table 4).

Discussion

Over the past several years, advances in the treatment of lung cancer have made the histopathological separation of the different types of lung carcinoma important to choose optimal treatment modalities.³ In view of these efforts, it becomes even more important to try to separate tumors that may show better clinical behavior from those that may follow a more aggressive clinical course. In addition, it is highly important to point out that tumor staging at the time of diagnosis plays an important role in the treatment and prognosis for patients. Thus, early diagnosis likely represents the most important parameter in terms of survival. In this setting, it is also important to mention that patients whose tumors are staged as T1N0M0 will be treated with complete surgical resection, either by lobectomy or wedge resection/segmentectomy, and close clinical follow-up. Patients with more advanced stages of the disease are likely to receive additional medical therapy.

In recent years, the term *bronchioloalveolar carcinoma* has been under scrutiny, and different views on the subject have been presented. Historically, the term has been under much debate and different views have been presented to attest to its clinical behavior without, however, producing a unifying agreement.^{4–19} In 1960, Liebow²⁰ introduced the term *bronchioloalveolar carcinoma* to describe a well-differentiated adenocarcinoma that may have long dormancy or slow growth, particularly in those patients presenting with isolated nodules. More recently and exclusively looking at the solitary nodule pattern, there have been proposals for a change in the nomenclature of pulmonary adenocarcinomas with a pure lepidic or bronchioloalveolar growth pattern. The first one of these suggestions was made in the 2004 WHO publication on Tumors of the Lung, Pleura, Thymus, and Heart.¹ In this publication, a few series of cases were cited that, according to the authors, provided the necessary evidence for such a change in terminology.^{21–24} Interestingly, close review of those citations shows that in some cases the ‘criteria’ imposed by the WHO authors were not actually met in the evaluation of the tumors presented. The main theory has been that owing to the indolent behavior by tumors with pure lepidic

Figure 4 (a) Kaplan–Meier survival curves comparing tumors with any lepidic component to those without. (b) Survival curves comparing tumors with a lepidic pattern divided by the percentage of the lepidic component (<25, 25–50, and >50%). (c) Survival curves comparing tumors with a lepidic pattern divided by the percentage of the lepidic component (≤50 and >50%). (d) Kaplan–Meier curve for tumors with a pure lepidic pattern (the so-called ‘*in situ* adenocarcinoma’).

growth, the 5-year survival is nearly 100%.²² However, such a view has generated some controversy.^{25,26} By following the criteria imposed by the WHO, various authors have obtained different results. For instance, Breathnach *et al*²⁷ in a study focusing on the survival and recurrences of bronchioloalveolar carcinoma stage I disease found that when comparing bronchioloalveolar carcinoma stage I and adenocarcinoma of the conventional type, the 5-year survival rate for bronchioloalveolar carcinoma is 83 and 63% for other types of adenocarcinoma. In a different study, Ebright *et al*²⁸ concluded that the most important predictors of

survival in bronchioloalveolar carcinoma are clinical and pathological stage rather than the degree of invasion on histological examination.

More recently, another change in nomenclature has been presented.² This time the authors suggested changing the nomenclature to two different terms: (1) *in situ* adenocarcinoma to describe those tumors previously known as *bronchioloalveolar carcinoma*, and (2) *minimally invasive adenocarcinoma* to describe those tumors with a predominant lepidic growth pattern and an area of minimal invasion (≤5 mm). This new proposal was based on a literature review rather than on an actual

Figure 5 Kaplan–Meier survival curve for 104 patients with T1N0M0 pulmonary adenocarcinoma.

Figure 6 Kaplan–Meier survival curve for 56 patients with T1N0M0 pulmonary adenocarcinoma and no associated malignancy.

Table 4 Statistical comparison of the survival probability of 104 patients with T1N0M0 pulmonary adenocarcinoma^a

n	12 m	24 m	36 m	48 m	60 m
104	0.951	0.922	0.852	0.818	0.802
56	0.982	0.964	0.909	0.889	0.863

Abbreviations: m, months.

^aWith associated malignancies compared with 56 patients without associated malignancies.

clinicopathological study. The authors stated that they had reviewed 11 thousand citations from which they selected 312 that ‘met specified

Table 5 Collected cases diagnosed as bronchioloalveolar carcinoma—T1N0M0

Author	No. of cases	Gross tumor size
Yamamoto <i>et al.</i> ²⁹	42	< 2 cm ^a
Watanabe <i>et al.</i> ³⁰	17	0.5–1.2 cm ^b
Suzuki ³¹	47	0.6–3.0 cm
Sakurai ³²	85	0.5–3.0 cm ^c
Yamada and Kohno ³³	26	< 2.0 cm ^d
Yoshida <i>et al.</i> ³⁴	50	0.2–2.1 cm
Koike <i>et al.</i> ³⁵	46	0.7–4.1 cm
Vasques <i>et al.</i> ³⁶	20	< 2 cm ^e
Yoshizawa <i>et al.</i> ³⁷	8	Not provided
Sakurai <i>et al.</i> ³⁸	25	0.5–3.0 cm
Yim <i>et al.</i> ⁴⁰	29	1.1 ± 0.45
Borczuk ⁴¹	8	1.4 ± 0.7
Noguchi <i>et al.</i> ²²	28	< 2.0 cm ^f

^aNo specific number of cases to a specific size was provided.

^bIn all, 16/17 tumors were under 1 cm, but no specific sizes were provided.

^cBronchioloalveolar carcinoma was subdivided into four different categories depending on stromal invasion.

^dThe authors mixed some cases of bronchioloalveolar carcinoma type A, B, and C with AAH (atypical adenomatous hyperplasia).

^eOnly one case diagnosed as bronchioloalveolar carcinoma was > 2 cm.

^fNo specific sizes were provided. The Materials and methods refer to 34 cases, some of them with vascular and pleural invasion.

eligibility.’ The citations supporting their notion, interestingly, have been presented as series of *bronchioloalveolar carcinomas* or small adenocarcinomas (< 2 cm)^{29–41} (Table 5). In some of these, the actual size of the tumor has been at best vague leaving the impression that some of these lesions may not even qualify as adenocarcinoma, but would rather have to be classified as atypical adenomatous hyperplasia (tumors with lepidic growth and size ≤ 0.5 cm). Nevertheless, the main idea concluded from these citations was that such a tumor behaves in an indolent manner, a feature that, according to the authors of that publication, qualifies these lesions to be renamed *in situ adenocarcinoma*.

In our study, we followed the criteria presented in those publications in terms of histopathological assessment of the tumors, mainly those now regarded as *in situ adenocarcinomas*. However, contrary to what has occurred in some of the series cited by the authors of the new proposal, we included all cases in which the stage was confirmed at T1N0M0. Our study includes 104 patients who met those specified criteria and in whom all the surgical resections, radiological, and pathological evaluations were performed in the same institution. Clearly, as expected in a cancer center, most of the patients were carefully monitored, mainly those patients in whom a previous diagnosis of malignancy had been established. Thus, among our patient population, 48 patients had a previous history of malignancy, while in 56 patients the pulmonary neoplasm was the only malignancy established. Univariable and multivariable statistical analyses looking at the clinical aspects, such as

type of surgery, age, gender, tumor size, and comorbidities failed to show any statistical significance with reference to clinical outcome. However, when we separated the patients into those with a previous history of malignancy and those without, we did encounter a statistically significant difference ($P=0.049$ on univariable analysis). In addition, statistical analyses of the cases by histological characteristics that included tumor differentiation and the percentage of the lepidic component did not show any statistically significant values in terms of survival. Therefore, based on our results, the differentiation of the tumor, which has been claimed as a predictor of tumor recurrence,⁴² is, in our opinion, not a reliable predictor of such, as none of our patients had recurrent disease during the specified follow-up period. We did, however, note a trend towards better prognosis, although not statistically significant, in all those tumors with a lepidic component ($P=0.058$). However, when we further substratified this group by proportion of the lepidic component, we encountered no statistically significant difference between lepidic tumors and non-lepidic tumors. Furthermore, we encountered only six cases in which the radiological findings were of a pure ground-glass opacity that correlated with six cases of pure lepidic growth pattern on histology. That in itself also casts some doubt as to the validity of that particular feature to identify cases with a lepidic histological growth pattern, as 13 additional cases showed histological evidence of pure lepidic growth. It is important to underscore the fact that currently, among other parameters, we are using the pathology gross size of the specimen to determine whether to label these tumors as *in situ adenocarcinoma* and not the radiological measurement of the tumor. Using the radiological tumor size would make more sense if we were attempting to avoid more radical procedures. Our follow-up information in the 56 patients in whom there was no other history of malignancy showed that seven patients had died after a median follow-up of 57 months. It is likely that these patients did not die of recurrent or widespread disease, even though we were not able to determine the exact cause of death.

On the basis of these results, we consider that the term *in situ adenocarcinoma* and *minimally invasive adenocarcinoma* are premature terms that may actually be misleading in the treatment of these patients. These terms should in no way deter surgeons from performing staging procedures in these patients, which brings us back to the use of the clinical significance of these terms. This fact is well illustrated by Takizawa *et al*,⁴³ who reported a study of 157 patients who underwent lobectomy and complete hilar/mediastinal lymphadenectomy for small peripheral adenocarcinomas between the sizes of 1.1 and 2.0 cm, and found that 17% of the patients had metastatic disease in lymph nodes. However, more interesting is the fact that 8% of

these tumors were coded as well-differentiated adenocarcinomas. Similar findings were also encountered by Konaka *et al*,⁴⁴ who reported 171 patients, 136 of whom had peripheral adenocarcinomas with a tumor size <2.0 cm. The authors found 22% of patients with lymph node metastasis in tumors between 1.5 and 2.0 cm, whereas no tumor metastasis was present in tumors <1.0 cm. They concluded that systematic mediastinal and lymph node dissection is necessary even for patients with a tumor size <2.0 cm.

Our results clearly reveal no statistically significant difference between all these groups, mainly lepidic and non-lepidic T1N0M0 adenocarcinomas, thus diminishing the importance of terms such as *in situ* or *minimally invasive adenocarcinoma*. On the basis of our results, we consider that the outcome for patients with T1N0M0 disease is still best determined by proper staging rather than by changes in the pathology nomenclature of adenocarcinoma. We also consider that more studies should be conducted with actual series of cases instead of merely performing a literature review before any change in the nomenclature is seriously considered. In addition, the choice of surgical treatment for these patients, whether lobectomy or wedge resection, should be made based on clinical and radiological grounds rather than making such a choice based on histology alone by tissue biopsy.

Hence, we suggest the following approach for adenocarcinomas on biopsy or resected specimens:

- On biopsy:
 - Adenocarcinoma with lepidic or bronchioloalveolar growth pattern (for tumors >0.5 cm).
- For resected specimens:
 - Adenocarcinoma with lepidic or bronchioloalveolar growth pattern (state the percentage of lepidic component present).
 - Size of the tumor.
 - Status of pleural integrity.
 - Status of lymph nodes.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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