European Respiratory Society/American Thoracic Society/International Association for the Study of Lung Cancer International Multidisciplinary Classification of Lung Adenocarcinoma

State of the Art

To the Editor:

The extensive work for a new classification of lung adenocarcinoma by Travis et al.[1] is highly appreciated. Nevertheless, new terms and definitions raise questions and discussions, which should be addressed in focus of the application of the new multidisciplinary classification of lung adenocarcinoma to clinical management of patients with lung cancer worldwide.

First, the inclusion of tumor size in solitary nodules (<3 cm and <5 mm invasion) into the new classification is questionable. A continuous development of preinvasive lesions into more extensive disease stages may occur, independent from the chosen size; furthermore, size is a prognostic relevant criterion within the existing tumor, node, metastasis (TNM) system which should not be replaced. In this context, the terms adenocarcinoma in situ and minimally invasive adenocarcinoma have a potential of misguidance, especially due to their limitation on resection specimens, which is not applicable to small biopsies and cytological specimens as well. Considering the aspect that also small simultaneous multilocular lesions may occur, the question arises, how multilocular synchronous lesions could be histologically distinguished from a solitary lesion in the proposed classification. The present term "bronchioalveolar carcinoma" is restricted to tumors with lepidic growth, or at least predominantly lepidic growth, and does not address size, solitary, or—synchronous—multiple location, which is expressed by the TNM formula, thus offering a clear classificatory description. Therefore, the relation between the clinical TNM system and the new classification has to be clarified to avoid an overlap f.e. in a T1a status according to the International Association for the Study of Lung Cancer 2007.[2]

For pneumologists in particular, small biopsies are frequently the basis for diagnosis, and a solution to render the vague new term "favor" (non-small cell lung cancer favor adenocarcinoma) more precisely could be the addition of a quality marker for histological or cytological diagnosis as it is available in the TNM system for the clinical use (C1–C4).[3] Using such an adjunct, no artificial separations between small and large biopsies or new terms would be necessary.

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Sublobar Resection of Ground Glass Opacity—Great Data, but can I have More?

To the Editor:

I read with great interest the article by Susuki et al.[1] and commend the authors for applying formal scientific methods in a prospective study to the issue of selection of patients for sublobar resection. These investigators and others from Japan have led the world in better defining the management of these patients. Nevertheless, I wish they had reported a few more details.

From a statistician's point of view, sensitivity and specificity are good measures, but these do not lend themselves well to prospective application to an individual patient, which is the problem faced by the clinician. Specificity tells us how often the radiographic assessment will be positive for invasion in a cohort of patients in whom it is already known that they all have invasion.[2] A clinician, of course, does not know whether the patient has or does not have invasion preoperatively and only knows that the radiographic assessment has been either negative or positive. Thus, the clinician needs to know how often the assessment of "radiographically noninvasive" is falsely negative. This requires knowledge of the false-negative (FN) rate of the test result (or, as some

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prefer, the less intuitive term negative predictive value). Although the FN or false-positive rate is sometimes criticized for being influenced by the prevalence, this effect primarily occurs at extremely high or low prevalence (not in the range of prevalence among the patients in this study). As I calculate the results for all patients (regardless of size), the FN rate is 5%, 9%, and 7% for the C/T ratio, tumor disappearance ratio, and visual estimation methods, respectively. I wish the authors would report the FN rates for the three methods for tumors less than 2 cm. They have not provided enough data to allow this calculation to be made.

In addition, although vascular invasion and lymphatic invasion have been widely viewed as surrogate markers for tumor dissemination to nodes or distant sites in Japan, this has been less well adopted in other parts of the world. Furthermore, I would argue that the issue in question is local spread (i.e. nodal metastasis) when considering lobar versus sublobar resection (if distant metastasis has occurred, it will not be influenced by the extent of local resection). Therefore, I think that focusing on a surrogate such as vascular or lymphatic invasion may not be as relevant as the actual occurrence of nodal metastasis. I wish the authors would specifically report the incidence of nodal involvement for tumors with a C/T ratio, tumor disappearance ratio, and visual estimation ratio of less than 0.5 (for lesions of all sizes as well as only those <2 cm).

Once again, I wish to commend the authors for their substantial contributions to the clinical science of lung cancer.

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TABLE 1. Radiologic-Pathologic Correlation in Lung Cancer 2.0 cm or Less in Size (Cutoff: 0.5)

	Pathological Diagnosis[b]	
Radiology (Cutoff: 0.5)[a]	**Noninvasive**	**Invasive**
Consolidation/tumor ratio on lung window		
Noninvasive[a]	65	2
Invasive	145	77
Sensitivity	31.0% (95% CI: 24.8–37.7)	
Specificity	97.5% (95% CI: 91.2–99.7)	
TDR		
Noninvasive[a]	101	10
Invasive	109	69
Sensitivity	48.1% (95% CI: 41.2–55.1)	
Specificity	87.3% (95% CI: 78.0–93.8)	
Visual estimation of consolidation		
Noninvasive[a]	84	7
Invasive	126	72
Sensitivity	40.0% (95% CI: 33.3–47.0)	
Specificity	91.1% (95% CI: 82.6–96.4)	

TDR, tumor disappearance ratio; CI, confidence interval.
[a] Cutoff for the diagnosis of radiologic noninvasive cancer is 0.5.
[b] Pathological noninvasive is defined as adenocarcinoma with no nodal involvement, lymphatic invasion, nor vascular invasion.

JCOG0201 Defined "Radiological Early Peripheral Lung Adenocarcinoma"

To the Editor:

In our article entitled, "A Prospective Radiological Study of Thin-Section Computed Tomography to Predict Pathological Noninvasiveness in Peripheral Clinical IA Lung Cancer (JCOG0201)," we made a comparison between radiological findings of ground glass attenuation on thin-section computed tomography and pathological invasiveness such as lymph node metastasis. Sensitivity and specificity were evaluated in this article, and the definition of radiological early peripheral lung cancer was clarified for the first time. It is difficult for readers to interpret those data because of its unique method and mode for defining radiological early lung cancer.[1] However, Dr. Detterbeck's question definitely hit the nail of the head. We agree with him on that most surgeons need information on lymph node metastasis instead of vascular or lymphatic invasion. We actually prepared the data for submitting, but it was not possible for the limitation of the number of the tables. As to the false-negative cases for invasiveness in lung cancer 2 cm or less in size, the following table is added (Table 1). This table contains data on lung cancer 2.0 cm or less in size and cutoff of 0.5, that is, the size of consolidation less than half of the maximum tumor dimension. As to nodal invasion for radiological early lung cancer, we are preparing manuscript on this matter. We are sure to submit the information in the near future.

In addition, we have already conducted phase II trial named JCOG0804 for limited surgical resection for the "radiological early lung cancer" defined by the JCOG0201. Accrual of patients has just been completed, and we will conclude whether our criteria for early lung

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