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Long-Term Follow-Up of Severe Dysplasia and Carcinoma In Situ of the Bronchus

To the Editor:

In a previous issue of the journal, Banerjee¹ brilliantly reviewed the available data from the literature about the natural history of bronchial preinvasive lesions. We congratulate the author for this very important and difficult work.

In his review, the author cited our work published in the American Journal of Respiratory and Critical Care Medicine in 2001² that described the 24 months follow-up of 416 preinvasive lesions in 104 patients. Indeed, we agree with the author's conclusions that limited individual lesion follow-up in most studies, as well as interferences with local or even systemic treatments, complicate the assessment of the potential aggressiveness of lesions known to be characterized by a long carcinogenesis process.

In a recent published work, not cited in Banerjee's review, we provided some answers to these limitations³ in studying the long-term evolution of 37 patients and 54 high-grade preinvasive lesions—31 carcinoma in situ (CIS) and 23 severe dysplasia (SD)—during a 12-year period. Our study was performed using auto-fluorescence bronchoscopy with repeated bronchial biopsy sampling over time, with a mean of seven biopsies per individual lesion during the follow-up and molecular analysis

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TABLE 1. Outcome of Bronchial Severe Dysplasia and Carcinoma In Situ According to the Molecular Analysis of the Lesion at Baseline

	Progression to Invasive Cancer	Tt R	Tt S	Regression	P
Lesions with at least one LOH	7/7	10/11	13/17	9/19	0.01 ^a
3p LOH	6/6	7/11	6/16	2/17	<0.0001 ^b
5q LOH	3/5	3/10	1/15	5/17	0.09 ^b
9p LOH	5/7	6/9	10/15	5/15	0.20 ^b

^a χ^2 test.

^b Fisher's exact test.

Tt R, treatment resistant; Tt S, treatment sensitive; LOH, loss of heterozygosity.

Modified from *Am J Respir Crit Care Med*. 2008;177:880–886.

of the baseline lesions. We believe that this very long monitoring authorizes to draw reliable conclusions on the aggressiveness of high-grade lesions, despite the fact that conservative endobronchial treatment was applied to persisting or relapsing lesions.

To reliably identify the factors that are linked to the lesions' evolution over time, we used a very restrictive definition of "progression," including local progression to invasive cancer. We also defined a locally treated lesion as "treatment resistant" that recurred at any time during the monitoring period and "treatment sensitive" those that did not reoccur after local treatment, whereas regressing lesions were those that spontaneously disappeared without treatment. This allowed us to classify accurately the more aggressive lesions in the progression or treatment resistant groups, while ascertaining that the spontaneously regressing lesions were truly benign ones (Table 1).

In this study, we observed that all the lesions that progressed to invasive cancer were initially classified as CIS (7 of 7) according to World Health Organization 1999 standards,⁴ and 10 of 31 CIS were resistant to several courses of endoscopic treatments, whereas 10 of 31 CIS were treatment sensitive and only 4 of 31 CIS spontaneously regressed without recurrence during follow-up. Our study also provided valuable information on long-term SD and CIS patients outcome, with, at the study end point, nine deaths attributable to lung cancer including four deaths directly related to the progression of the initial high-grade bronchial lesion. In addition, using careful laser microdissection and robust molecular analysis on the baseline lesions,^{3,5} we could demonstrate that

losses of heterozygosity (LOH) of chromosome 3p and 9p are significantly more frequent in CIS compared with SD, whereas 3p LOH seems to be a strong predictor of progression in the whole group of lesions and in the CIS group (Table 1).

Altogether, our results lend strong support to the World Health Organization classification for the premalignant bronchial lesions, which clearly differentiates CIS from SD,⁴ not only in confirming their different outcomes, as we had previously observed,² but also in providing evidence of significant differences at the molecular level.

Finally, our contribution shows that CIS histology as defined by 1999 WHO classification and the molecular analysis of 3p LOH are useful indicators of the evolution of high-grade preinvasive bronchial lesions. The molecular analysis could easily be integrated in the management decision tree of CIS and SD of the bronchial epithelium.

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