Editorial Commentary

Obstructive lung disease in smokers and never smokers: further insights in patient-related approach in lung cancer understanding

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Although smoking still represents the leading cause of lung cancer, obstructive lung disease is another independent risk factor. In chronic obstructive pulmonary disease (COPD), a systemic inflammatory disorder with specific tumor immune environment, this risk is two- to five-fold greater compared with smoking without COPD (1,2). Thus, when managing patients with non-small cell lung cancer (NSCLC) for curative treatment, (surgery, but also immune check points inhibitors in non-surgical patients), associated COPD should be taken into account, because of increased post-operative risk (3-6) on one side, but possible increased efficacy of anti PD1/PDL1 immunotherapy (7).

Smoking is also the main causative factor of COPD, but non-smoking-related Obstructive Pulmonary Disease is more and more frequent; its exact incidence in never smokers with resectable non-small cell lung cancer is not known, but is probably extremely variable among different epidemiological contexts. In a previous prospective observational study of my team (POFE: Postoperative Outcomes of Frequent Exacerbators Chronic Obstructive Pulmonary Disease patients after resection of Non-Small Cells Lung Cancer) (8), we showed that among 682 patients with suspected or proven operable lung cancer admitted in our thoracic surgery department in a 17-month period, 114 (16.7%) had COPD and 93 of them had final diagnosis of non-small cell lung cancer. In our study, the great majority of COPD patients (97%) were current or former smokers and only half of them had stopped tobacco consumption before the operation, despite specific measures, including incitation and anti-tobacco consultation (8).

In the recent paper of Akamine *et al.* in the *Interactive Cardiovascular and Thoracic Surgery* (9), obstructive pulmonary disease, defined as FEV1/FVC <70% was found in 20% of never smoker patients with lung cancer undergoing surgery. Of course, study design and flow-charts of ours' (8) and Dr Akamine's study (9) are not comparable; however it seems intuitive that the epidemiological context (Asian versus European populations) is probably responsible for the observed differences. Anyway, as acknowledged by the authors, obstructive pulmonary disease was not diagnosed on the basis of the Global Initiative for Obstructive Lung Disease (GOLD) criteria, requiring post-bronchodilator assessment of FEV1/FVC ratio, but on the sample finding of FEV1/FVC <70%, regardless of the use of bronchodilators before spirometry: of note 58% of non-smokers and 44% of smokers with obstructive pulmonary disease had their spirometry performed without bronchodilators. This prompted the authors to use the term of obstructive pulmonary disease rather than COPD. Thus other obstructive conditions (especially, but not only, bronchial asthma) are probably included in the populations of operated obstructive pulmonary disease of the quoted study (9), and the relative contributions of these other obstructive diseases and true COPD is probably more important among the non-smokers. Furthermore,

information on passive smoking was not collected in this retrospective study (9).

The most important finding of the large-scale study of Akamine and co-workers (9) was that obstructive pulmonary disease in never smokers was an independent negative prognostic factor, differently from COPD in smokers. The authors suggest two possible explicative mechanisms (which are merely speculative in their study and would deserve specific studies), namely a lower socio-economic status in never smokers with obstructive pulmonary disease and an increased frequency of mutated PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), this mutation being associated with a negative outcome (10).

Although the independent negative prognostic significance of obstructive pulmonary disease in never smoking was confirmed at multivariable analysis, it should be pointed out that in the study of Akamine *et al.* (9), the proportion of women and adenocarcinoma patients was significantly higher in the group of never smokers compared with smokers, and, among the 261 patients whose EGFR status was known, mutations were significantly more frequent among the never smokers. On the other hand, among never smokers, and differently from smokers, patients with obstructive lung disease had more frequently higher T status, presence of pleural invasion and vascular emboli (9), suggesting that this particular phenotype of patients with lung cancer is associated with biologically more aggressive disease. Indeed, when looking at survival curves (both recurrence-free and cancer-specific survival), non-smokers with obstructive pulmonary disease had the less favorable outcome.

Anyway, the study of Akamine *et al.* seems to confirm the concept that variables linked to patient phenotype are important determinants of outcome of resectable lung cancer as well as variables linked to disease itself, and that variables linked to patients and to tumor are often related, underlining the complex interplay between host and disease (11,12). In my opinion tumoral immune microenvironment, in terms of structure, density and function, represents the effector of this continuous interplay in which periods of antitumor activity and inactivity continuously succeed one another (11,12).

In a retrospective analysis of a prospectively collected database on 303 patients with resected NSCLC, I and co-workers (13) reported that chronic bronchitis was associated with worse long-term overall survival; a trend toward worse survival was also observed in COPD. In that study, 87% of patients were current or former smokers and survival was not analyzed with respect to combined functional status and smoking habit, preventing comparison of our results with Akamines's ones (9), which would be anyway difficult because of epidemiological differences. In that study (13), we observed that chronic bronchitis and, even more, COPD were inversely correlated with the count of mature dendritic cells in tumor microenvironment, whose higher number, together with higher number of CD8+ T lymphocytes, was associated with improved long-term survival. More recently (14), in a study focusing on a consecutive series of 503 patients with resected pulmonary adenocarcinoma, we found that COPD was associated with worse prognosis together with age more than 65 years, extent of resection, pathologic stage, T size, T and N variables, and presence of vascular or lymphatic emboli.

Focusing on outcome of COPD patients with associated lung cancer undergoing resection (7), we observed that COPD severity is positively correlated with the co-expression of PD-1/TIM-3 (T-cell immunoglobulin and mucin domain-containing molecule-3) by CD8 T lymphocytes, a marker of CD8 exhaustion. In agreement, we observed a loss of CD8 T cell-associated favorable clinical outcome in patients with COPD undergoing resection for NSCLC. Interestingly, a negative prognostic value of PD-L1 (programmed cell death ligand 1) expression by tumor cells was observed only in highly CD8 T cell-infiltrated tumors of COPD patients.

Interestingly, when analyzing data obtained on 39 patients with advanced-stage non-small cell lung cancer treated by an anti-PD-1 antibody, we showed longer progression-free survival in COPD patients, and also that the association between the severity of smoking and the response to nivolumab was preferentially observed in COPD patients (7).

In our studies COPD patients were mainly smokers and it would be interesting to study function of immune environment in never smokers with NSCLC [as in the study of Akamine *et al.* (9)] as well as in patients considered as never smokers but having history of passive smoking or exposition to other inhaled carcinogens. Together with molecular analysis on lung cancer in never smokers, this could provide further insight in tumor-host interaction in this subset of lung cancer patients.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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