



Relationship between obstructive lung disease and non-small cell lung cancer

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We would like to thank Dr. Alifano for his valuable comments on our study about the prognostic impact of obstructive lung disease on the survival of never smokers with resected non-small cell lung cancer (NSCLC) (1,2).

Several studies have investigated the impact of chronic obstructive pulmonary disease (COPD) on the prognosis of patients with NSCLC. We can expect that patients with COPD have worse prognosis than those who do not. This may be due to the high risk of death from diseases other than lung cancer, such as chronic respiratory disease and cardiovascular disease. Therefore, we investigated the effect of obstructive lung disease on cancer-specific survival of lung cancer in our study (2).

Recently, a meta-analysis (n=10 studies) demonstrated that there was no significant difference in post-operative survival in early-stage lung cancer between patients with and without mild-to-moderate COPD (3). In this review, there was also a subset analysis of the National Lung Screening Trial. This subset was composed of high-risk smokers who were screened and followed up after detection or treatment of lung cancer. The analysis revealed that the overall 5-year survival after surgery of early-stage NSCLC in smokers with and without COPD was not significantly different (84 and 81% respectively, P=0.65) (3). These data were consistent with our data showing that airflow limitation or obstructive lung disease did not affect cancer-

specific survival in smokers with NSCLC (2).

As Dr. Afiliano mentions, consideration of epidemiological differences is important in understanding the analysis of patients' prognosis with COPD or NSCLC. As smoking prevalence varies in different nations (4), we fully agree with this opinion. Thus, epidemiological differences may influence the results of the systematic review described above.

We demonstrated that obstructive lung disease was an independent prognostic factor in never smokers with NSCLC (2). As Dr. Alifano states, our data may indicate that host status influences the tumor's immune microenvironment, which leads to a more aggressive biological phenotype. Recently, alterations in the tumor immune microenvironment in NSCLC caused by COPD, especially regarding immune cell composition, have been reported. Alifano and coworkers showed that exhausted CD8 tumor-inflating T lymphocytes, which lead to cancer immune escape, were exacerbated in COPD patients with NSCLC (5). Furthermore, Mark *et al.* observed increased Th1 lymphocytes in both the lung and tumor immune microenvironment in COPD patients with NSCLC (6). Interestingly, they also demonstrated that the presence of COPD is associated with an improved response to immune checkpoint inhibitors (6). Therefore, we can expect that the tumor immune microenvironment may have important

therapeutic implications.

As Dr. Afiliano highlighted, these studies are mostly focused on COPD patients who smoke. The epidemiology of smoking has changed and the proportion of never smokers with NSCLC has been increasing (7). Based on the comments of Dr. Afiliano, we would like to perform a molecular analysis of the tumor immune environment of never smokers with NSCLC for further insights into tumor–host immune interactions.

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Footnote

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