Lung Cancer 131 (2019) 155–156

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Response to comment on: 'Synchronous multiple non-small cell lung cancers in an allograft lung recipient'

Sir,

We thank Dr P. Baas et al. for their letter. In their comments, they attracted the "Lung Cancer" readers' attention on the difficulties in proposing orthotopic pulmonary transplantation for patients with terminally-ill respiratory diseases and they gave the limits for an acceptable lung graft, defined as a lung with negative bacterial sampling, with standard chest roentgenography, and coming from a donor with no more than 20 pack-year tobacco smoking history.

Pulmonologists and oncologists, all know the scarcity of lung grafts, and the sorrowful imbalance in the number of available transplants and the number of potential recipients [1]. Therefore, transplantation teams must be recognized for their tireless efforts to propose grafts for patients with no other perspective than lung transplant and subsequent immunosuppressive treatment, in an emergency context. In consideration with the various life-threatening-adverse events possibly affecting a lung transplant recipient, one can hypothesize that lung cancer occurring in lung transplant is an underestimated complication that would merit a competitive risk approach to be clearly evaluated. Hitherto, many studies have shown that, both donor and recipient smoking increases graft loss and mortality in solid organ transplant recipients [2].

By essence, a case report has limited conclusions. Nevertheless, the very early occurrence of multiple synchronous lung cancers in a 39-year old non-smoker lung transplant recipient, together with the genotypic profile of developing lung cancers (squamous-cell lung cancer and non-otherwise specified non-small cell lung cancer [NSCLC], with oncogenic addiction to a $KRAS^{G12A}$ mutation), and the dynamic growth of the tumors in a young woman receiving immunosuppressive therapy, have highlighted the putative mechanisms of lung cancer occurring on lung transplants [3]. The particularities of this case report, that might be relevant warnings, even when donors are less than 20 pack-year smokers, are as follows: (i) the non-negligible probability of early occurrence of pre-neoplastic lesions such *in situ* adenocarcinoma bearing a *KRAS* mutation during life of donors with history of decades exposure to tobacco carcinogens, (ii) the unfavorable prognosis of *KRAS*-mutant NSCLC [4], and (iii) the accelerated development of cancers in patients receiving immunosuppressive therapy for solid organ transplantation [5].

In the native lung of smokers, several studies suggested that *in situ* adenocarcinoma or atypical alveolar hyperplasia grow at a tumor doubling time as long as 600 to over 1000 days [6]. In the herein case report, the growth of tumors was observed at a rate rarely seen in thoracic oncology, with no more than 24 months expended since the first radiographic finding of ground glass opacity, until terminally-ill stage and a doubling time of 28 days similar to the more aggressive small cell lung cancer. A similar accelerated tumor promotion toward metastatic phenotype has been observed in patients who underwent orthotopic liver transplant for hepatocellular carcinoma and consequently treated with immunosuppressive drugs: once these patients experienced metastatic relapse, the growth of lung metastases are observed at higher rate when compared with patients suffering from lung metastases after having underwent hepatic resection and therefore not receiving immunosuppressive treatment [7].

Therefore, one can doubt that when considering a putative donor, the "a smoking history of less than 20 pack-year" would be a sufficient guarantee. Regarding smoking-induced lung cancer-risk, the form of dependence of smoking dose is more in relationship with the duration of smoking rather that the crude quantity of cigarettes by day [8]. The dose-response relationship curve has no threshold and the lung cancer risk is already substantial for subject smoking 10 cigarettes/day [8]. Furthermore, most of the gene mutations opening the pathway to tumor cell promotion, tissue invasion toward tumor heterogeneity and metastatic phenotype (such as *P53*, *MET*, and *BRAF* mutations) are early events in carcinogenesis of the lung epithelium under genotoxic exposure. Multiregion whole-exome sequencing allows segregating clonal and subclonal mutations occurring in the phylogenetic tree of lung tumors; in this context, TP53 mutations were predominantly clonal and occur early for all subtypes of non-small cell lung cancer [9]. These genotypic alterations might lead to preclinical disease, subsequently boosted by immune-suppression, and might only result in tenuous roentgenographic abnormalities such as ground glass opacities not so easy to detect.

Recently, several studies suggested that liquid biopsy with exome analysis of circulating free DNA allows detection of minimal residual disease in patients who underwent complete resection of NSCLC [10]. Such a technique should be applied in the context of donors with smoking history. We suggest that transplantation teams might cooperate with oncologists in order to prospectively evaluate the risk of lung cancer developing in lung transplants coming from donors with more than a decade of tobacco exposure. This might be a pathway to improve the safety of lung transplantation and increase our knowledge of lung cancer risk in lung transplant.

Conflict of interest

None.

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DOI of original articles: https://doi.org/10.1016/j.lungcan.2018.07.024, http://dx.doi.org/10.1016/j.lungcan.2019.02.018

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Received 14 March 2019

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