Letter to the Editor

Morphologic characteristics of pulmonary adenocarcinomas manifesting as pure ground-glass nodules on CT

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Response to: Cohen JG, Ferretti GR. Pure ground-glass nodules: are they really indolent? J Thorac Dis 2017;9:2839-42.

Milanese G, Sverzellati N, Pastorino U, *et al*. Adenocarcinoma in pure ground glass nodules: histological evidence of invasion and open debate on optimal management. J Thorac Dis 2017;9:2862-7.

Peikert T, Rajagopalan S, Bartholmai B, *et al*. While size matters—advanced "Radiomics" remain promising for the clinical management of ground glass opacities. J Thorac Dis 2017;9:3568-71.

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We would like to thank the authors of the three editorials (1-3) for their interest in and comments on our article "*Lung Adenocarcinoma Manifesting as Pure Ground-Glass Nodules*: *Correlating CT Size*, *Volume*, *Density*, *and Roundness with Histopathologic Invasion and Size*" (4). In this article, we aimed to quantify computed tomography (CT) size, volume, density, and roundness of lung adenocarcinomas manifesting as pure ground-glass nodules (GGNs) on CT as measured on pre-resection CT scans, and to correlate these parameters with histologic features of invasiveness (4). We found that the correlations between size and number of histologically invasive foci with CT size were similar to the correlations with volume, and stronger than the correlations with CT density, and roundness of the nodule. We also found that invasive foci can be present in up to 17% of adenocarcinomas manifesting as pure GGNs on CT and smaller than 10 mm. We concluded that measuring volume and density of pure GGNs on a single pre-resection CT scan provides no advantage over two-dimensional size measurements, which appear sufficient for risk estimation in clinical practice (4). We also concluded that the risk of invasiveness in pure GGNs smaller than 10 mm should not be disregarded (4).

The authors of all three editorials emphasize the importance of accurate non-invasive pre-treatment risk stratification of pure GGNs to allow for optimal patient management (1-3). Malignant pure GGNs most commonly represent lesions from the lung adenocarcinoma spectrum, namely adenocarcinoma in situ, minimally invasive adenocarcinoma and invasive adenocarcinoma as defined by the IASLC/ATS/ERS (5). They often have an indolent clinical course, with a good prognosis. CT surveillance is a diagnostic option and invasive tissue sampling via surgical resection may lead to an increase in morbidity, mortality and health care costs (3). However, Cohen *et al.* emphasize that, contrary to other opinions, the risk inherent to pure GGNs should not be underestimated, as they can represent invasive adenocarcinomas where a more aggressive approach is needed (1).

In their editorial, Milanese *et al.* summarize previously reported morphological parameters for risk stratification of pure GGNs, beyond those reported in our own study (2). Those parameters include qualitative parameters, such as air bronchograms and normality of an adjacent vessel, and

quantitative parameters, such entropy and mass (2). They discuss the applicability of those parameters and their current limitations with respect to clinical practice (2). Both, Milanese *et al.* and Cohen *et al.* confirm our opinion that in the assessment of pure GGNs on a single CT scan, two dimensional CT size, as recommended by current guidelines (6-8), may be sufficient for clinical risk estimation (1,2). They also confirm that more sophisticated parameters such as volume, density, and roundness may play a lesser role (1,2). The practical advantage of two dimensional size measurements is indeed that they are easy to perform and readily available on every PACS workstation. This aspect of our findings, thus, has immediate practical implications. However, future longitudinal follow-up studies with these parameters investigated will show if they can provide useful incremental information with regard to prognosis and outcome (1,2).

In addition to these points, Peikert *et al.* emphasize the need for a more personalized treatment approach to risk stratification by assessing pure GGNs with the help of novel texture-based software (3). As an illustrative example they discuss the "Computer Aided Nodule Analysis and Risk Yield (CANARY)" software. This software uses density based information obtained from a single CT examination for classifying patients with lung adenocarcinoma into one of three prognostic groups. In several studies including one by our group, this software has provided promising results (9-12). Despite those early findings, however, many more questions need to be answered when it comes to the utilization of software and before it can become part of the daily clinical workflow. Such questions, for example, would be on reproducibility, the precise effect of different CT acquisition parameters, performance in different histologic entities, its applicability in longitudinal follow-up, and the determination of intervention thresholds.

Overall, we do agree with all the points raised by the authors of the three editorials. The number of editorials related to our article mirrors the general interest in the topic of pure GGNs. These editorials, however, could also suggest that our manuscript raises more questions than it provides answers, which, at the end of the day, would not be surprising. Indeed, the concept of pure GGNs is relatively young and rapidly evolving, and the available scientific evidence increases rapidly. This evidence is often apparently equivocal, as multiple factors that are difficult to control for, such as gender and geographic origin, can substantially influence the findings of individual studies on pure GGNs. Therefore, each incremental advance in knowledge in this field is of importance, and we thank the authors of the three editorials for raising relevant questions, notably related to paradigm shifts in the assessment of pure GGNs and the evaluation of their clinical outcome. These will, without doubt, stimulate further research in this interesting and clinically relevant area.

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Footnote

Conflicts of Interest: Dr. Heidinger is the 2016 Sven Paulin Research Fellow in Cardiothoracic Imaging at the Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts. Dr. Costa reports grants from Pfizer and personal fees from Ariad and Boehringer Ingelheim outside the submitted work. Dr. VanderLaan reports personal fees from Gala Therapeutics outside the submitted work. Dr. Bankier reports personal fees from Elsevier Publisher, the American Thoracic Society, and Spiration and Olympus outside the submitted work. The other authors have no conflicts of interest to declare.

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