Editorial

Pure ground-glass nodules: are they really indolent?

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Ever since the results of the ELCAP study (1), which reported the malignancy rate of subsolid nodules to be about 5 times higher than that of solid nodules, it is common knowledge among radiologists and pulmonologists that these specific nodules require special attention and management.

Malignant subsolid nodules mostly correspond to the spectrum of lung adenocarcinomas, which consists of three subtypes as defined by IASLC/ETS/ERS (2) and WHO classifications of lung tumors (3). Adenocarcinoma *in situ* and minimally invasive adenocarcinoma, which are defined on pathology by no invasive component and an invasive component of less than 5 mm, respectively, have shown an excellent prognosis with a 5-year survival after surgical resection reported to be between 98% and 100% (2,4). Prognosis is less good however for invasive adenocarcinomas, defined on pathology by an invasive component of more than 5 mm, stressing the need for more invasive management strategies.

Pure ground-glass nodules (pGGNs), which are defined by opposition to part-solid nodules by the absence of a solid component on CT, have first been thought to correspond mostly to benign or very slowly evolving lesions and thus been discarded by some physicians. However, recent studies have proven that those nodules often correspond to invasive adenocarcinomas, representing for example 39% of the nodules in a Korean series of 46 pGGNs (5) and 40% in a Chinese series of 94 pGGNs (6). This makes pGGNs a very different entity in comparison to part-solid nodules, which show by contrast good radio-pathological correlations between solid component on CT and invasive foci on pathology for nodules corresponding to adenocarcinomas (7,8), putting aside a few false positive of solid component on CT such as alveolar collapses, fibrotic scars or mucinous components (9,10). This significant overlap in imaging features of in situ/minimally invasive and invasive adenocarcinomas manifesting as pGGNs on CT, as shown in *Figure 1*, can be explained by several reasons. On the one hand, the limited resolution of CT scan may hinder detection of small invasive foci (11). On the other hand, specific adenocarcinoma subtypes, such as papillary or micropapillary adenocarcinomas, can display large invasive foci punctuated with aerated areas, which may therefore appear on CT as a ground-glass areas instead of solid components.

According to the difference of prognosis between AIS/MIA and invasive adenocarcinomas, it is critical to differentiate those lesions non-invasively so as to allow optimal management for patients. The first step when discovering a pGGN is, according to the latest guidelines (12), to control it by CT 6 to 12 months later, enabling to exclude from 33% to 67% of benign inflammatory and infectious lesions manifesting as pGGNs (13,14). Once this step is done, the main issue we have today is that the tools currently available to differentiate extremely slow growing *in situ* or minimally invasive lesions from faster growing invasive adenocarcinomas in persistent pGGNs remain relatively limited. Aside from the historic nodule size criteria, which remains the most used and validated (12), other criteria such as lobulated margins, tumor/lung interface, lobulated contours, and nodule attenuation were suggested, but struggle to reach consensus due to varying results among

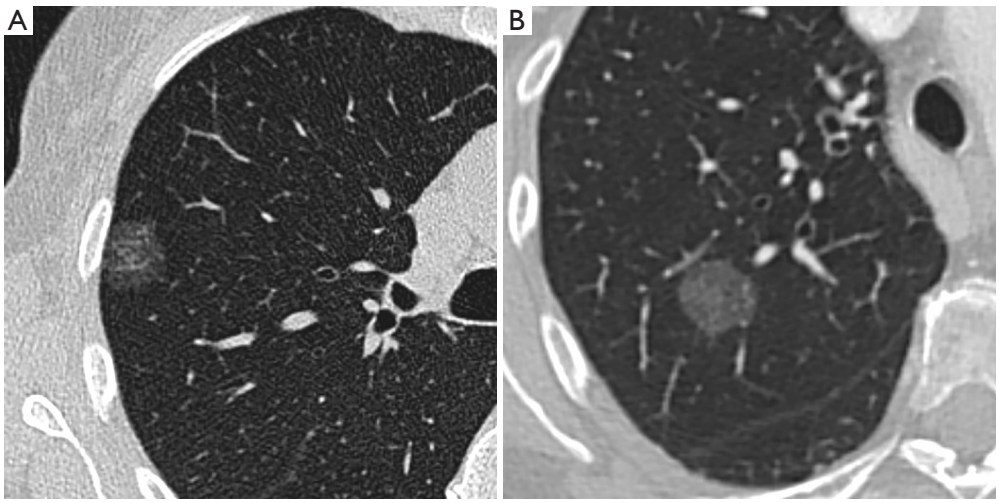

Figure 1 Imaging features overlap between different grades of lung adenocarcinomas presenting as pure ground-glass nodules. Chest CT scans displayed with lung window show respectively: (A) a pGGN of 20 mm in a 70-year-old female confirmed as an adenocarcinoma in situ; (B) a pGGN of 21 mm in a 66-year-old female patient confirmed on pathology as an invasive adenocarcinoma. pGGNs, pure ground-glass nodules.

different studies (6,15). In order to put light on this question, Heidinger *et al.* analyzed in a recently published study the relationship between pGGNs' diameter, volume, attenuation, roundness and the size and number of invasive foci, as well as age and gender of patients (16). The main conclusion of the authors of this study was that among all the existing criteria on a single CT, nodule diameter wasn't significantly less correlated with size and number of invasive foci on pathology than were attenuation, volume or roundness, and may therefore be sufficient alone for pGGNs' risk evaluation. This result may be valuable since diameter is a simple measurement and, while advanced measurement techniques such as semi-automatic segmentation have significantly developed for subsolid nodules (7,17) and are now usable in clinical practice, many centers are still not properly equipped.

There are however a few concerns and limits for the use of the largest diameter of the nodule as a single criterion. Indeed, as Heidinger *et al.* stress in their article (16), the largest nodule diameter shows at most a weak statistical correlation with the number and size of invasive foci on pathology. For this reason, in routine practice, CT follow-up and evaluation of nodule growth is one of the best tools to evaluate pGGNs' invasiveness. Similarly to what happens with solid nodules, 2D size alone may not be the best criteria to evaluate growth in pGGNs, which are known to have much slower volume doubling times than their solid counterparts. Even for subsolid nodules corresponding to adenocarcinomas, reported doubling times are of 813±375 days for pGGNs (18), i.e., much higher than those found in solid lung cancer nodules, with a median volume doubling time of 98 days (19). Furthermore, it is known that pGGNs may not only increase in size, but also in attenuation with or without appearance of a solid component, which are also risk factors of invasive lesions (20). Thus, while volume, attenuation and mass may not be more useful than a simple diameter for prognosis evaluation on a single CT, the situation may be quite different when it comes to follow-up.

The investigation of multiple invasive foci in the latter study (16) is an interesting endeavour. Indeed, current classifications are based on the largest invasive foci for the pathologist, and on the largest solid component on CT for the radiologist in the case of part-solid nodules. This raises the question to know how the number of invasive foci might affect lesion aggressiveness and patient prognosis compared to the size of the largest invasive foci. Further research is needed to properly answer this question.

Coming back to routine clinical practice, the Fleischner society recently released its 2017 guidelines for subsolid nodules (12), where axial diameter is also a key factor for pGGNs' management. According to these, pGGNs of less than 6 mm shouldn't warrant any particular follow-up, although an alternative of 2 and 4 years follow-up is proposed for pGGNs close to the 6 mm threshold and judged more suspicious. This is to reflect the results of a recent Japanese study (21) which showed that among

439 pGGNs of less than 5 mm, 10% eventually grew and 0.9% turned out to be adenocarcinomas, half of them invasive. For nodules larger than 6 mm, the guidelines propose follow-up CTs at 2 and 4 years after the first 6–12 months control CT and to refer patients for surgery in the case of significant growth and/or appearance of a solid component. The rational for those 2 years follow-up interval is that according to current data, a pGGN takes on average 3 to 4 years to grow and/or develop solid component (12).

In the future, emerging techniques may help us to further differentiate these lesions. Texture analysis may play a role in those advances and enable us to extract some additional features from those pGGNs. Although the effect of CT protocol parameters and different CT vendor/model on texture parameters remain an issue, several studies showed that parameters such as homogeneity and entropy might help differentiate invasive lesions in pGGNs (22,23). The constant evolution of semi-automatic segmentation and computer-aided techniques, may also be of use in the evaluation of those nodules, by reducing interobserver variability, enabling to more reliably differentiate pure and part-solid nodules and increasing the sensitivity of detection for small changes during follow-up.

As a conclusion, pGGNs shouldn't be underestimated as they correspond to invasive adenocarcinomas in up to 40% of cases. According to current guidelines and recent studies, it is still recommended to use the largest diameter of the nodules for their evaluation, although the diagnostic performance of this criterion to identify invasive adenocarcinomas remains moderate at best. Further research is needed to identify more efficient diagnostic criteria for stratifying the risk in pGGNs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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