Editorial

Differentiation of persistent pulmonary subsolid nodules with a solid component smaller than 6 mm: to be invasive adenocarcinoma or not to be?

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As the utilization of low-dose chest computed tomography (LDCT) has increased in daily clinical practice, many physicians and radiologists often encounter persistent pulmonary subsolid nodules (SSNs) (1,2). Extensive research has explored the clinical, radiological, and pathological characteristics of SSNs, significantly advancing our knowledge of this category of pulmonary nodules (3-5). As a prime theme on pulmonary SSNs, accurately differentiating pulmonary invasive adenocarcinomas (IACs) from minimally invasive adenocarcinoma (MIA)/preinvasive lesions using CT examinations is of vital importance, since this distinction can determine the management of patients with those nodules. Specifically, early-stage lung cancers, which pathologically represent MIA/preinvasive lesions and radiologically manifest as SSNs with a solid component <6 mm in most cases, may be removed through limited resection instead of lobectomy, which is the surgical standard for lung cancer (6,7). Furthermore, the policy of conservative management with regular CT follow-up as long as SSNs remain stable, with surgical resection performed if they grow, is increasingly accepted in medical communities (3,8,9). The key issue in this management strategy is that only highly invasive lesions such as IACs should be surgically resected, while MIA/preinvasive lesions may be managed through follow-up examinations, eventually improving patients' prognosis and avoiding unnecessary surgery (3,9). However, it is challenging to distinguish between IACs and MIA/preinvasive lesions through imaging studies alone because substantial overlap exists between these two categories (10,11). A large body of research has explored this topic, using a variety of analytic methods including qualitative and quantitative assessments (12-14), radiomics-based assessments (15,16), and in recent years, deep-learning algorithms (17,18).

Recently, Qi *et al.* published an interesting study on the differentiation of IACs from MIAs/preinvasive lesions in SSNs with a solid component <6 mm, including pure ground-glass nodules (PGGNs) and part-solid nodules (PSNs), using both qualitative and quantitative imaging features on CT (19). They evaluated 316 surgically-resected SSNs (260 PGGNs, 47 PSNs with a solid component < 6 mm, and 9 SSNs with cystic airspaces) from 287 patients. Excluding the SSNs with cystic airspaces, 307 SSNs were dichotomized according to whether they were IACs (n=195) or MIA/preinvasive lesions (n=112). The authors found that the mass of SSNs was the only significant feature differentiating IACs from MIA/preinvasive lesions, and 283.2 mg was the optimal cutoff value for distinguishing IACs from MIA/preinvasive lesions.

The result that the mass of SSNs was the only significant factor differentiating IACs from MIA/preinvasive lesions (19) is in line with previous studies (20,21). However, there are substantial differences in the optimal cutoff value among those studies (283.2 mg in the study of Qi *et al. vs.* 386 mg

in the study of Liu *et al.*, and 472 mg in the study of Lim *et al.*) (19-21). As Qi *et al.* commented (19), it can be speculated that this discrepancy is due to differences in the populations of each study. While Qi *et al.* included SSNs with a solid component <6 mm, including both PGGNs and PSNs, Liu *et al.* and Lim *et al.* only included PGGNs in a mass-related analysis; in particular, Lim *et al.* analyzed SSNs measuring 10 mm or larger (19-21). However, it is well known that the CT features of IACs and MIA/preinvasive lesions can overlap substantially (10,11). In fact, IACs can appear as SSNs <10 mm, and MIA/preinvasive lesions can present as PSNs (4). Therefore, studies dealing with IAC, MIA, and preinvasive lesions should include all SSNs regardless of size and type, and the study of Qi *et al.* has strength in this point (19). However, as every study has its own strengths and weaknesses, Qi *et al.* study also had their weaknesses. One of them is the lack of validation of their results with independent test cohorts. So, they still need more work to confirm whether the mass value of SSNs on CTs would differentiate IAC from MIA/preinvasive lesions (19).

Despite the non-significant findings of the multivariate binary logistic analysis, morphological features (lobulated or spiculated margins, the presence of vacuoles or air-bronchograms, and pleural tag/pleural indentation) and SSNs' mean diameter were significantly different between IACs and MIA/preinvasive lesions in the univariate analysis (19). Concordantly, these characteristics are well-known differentiators of IACs from preinvasive lesions (3,12). However, it should be kept in mind that intra- or inter-reader variability was not evaluated for these factors by Qi *et al.*, even though evaluations of morphological features and measurements of nodule diameter are vulnerable to inter- and intra-reader variability, especially for small SSNs (22). In contrast, three-dimensional (3D) image features are known to be less sensitive to intra- or inter-reader variability (22), and fortunately, the mass of the nodules, which was the only significant differentiating factor between IACs and MIA/preinvasive lesions found by Qi *et al.*, is one of these 3D image features.

Meanwhile, for studies dealing with nodule measurement, it should be emphasized that researchers should consider potential factors resulting in image variability, and readers should understand the possibility of variability between or within the studies. The prime examples are measurement methods (e.g., handcraft measurements, semi-automatic measurements, and automatic measurements), the type of software used for measurement or segmentation, the use of contrast media, image data reconstruction (e.g., section thickness), and display window settings (3,22). In this study, SSNs were automatically measured with a commercially available software in the lung window setting and the reconstruction thickness was 1.0–1.25 mm, which is the optimal section thickness for analyzing SSNs (19). However, CT images both with and without contrast media were analyzed by Qi *et al.* (19), and this heterogeneity should be understood as a cause of imaging variability between SSNs.

Interestingly, Qi *et al.* compared the associations of pathological subtypes of IACs with various clinical and radiological features. Papillary IACs had a higher mass than that of lepidic or acinar IACs, though the difference did not reach statistical significance (19). Since patients with papillary IACs were found to have shorter disease-free survival than those with lepidic or acinar IACs (23), the mass of SSNs may be correlated with patients' outcomes, demonstrating its potential as a prognostic factor. This hypothesis is supported by the results that IACs had a higher mass than that of preinvasive lesions (19), and the proportion of the solid component, which is a prognostic indicator in SSNs, was significantly different between IAC subtypes in a prior study (24). Further analyses need to be conducted to determine the relationship between the mass of SSNs and patients' survival.

With advances in computer science, various state-of-the-art technologies have been applied to differentiate IACs from MIA/preinvasive lesions (15,16). One of these technological frameworks is radiomics, which is a method of quantitative imaging analysis that investigates the attenuation values of each voxel and their distribution within target lesions, translating the results into clinical meaningfully conclusions (15,16). In prior studies, smaller nodule mass was a significant differentiator for MIA/preinvasive lesions from IACs in both PSNs and PGGNs (15,16). In addition, higher kurtosis in the PSN group and lower entropy and higher homogeneity in the PGGN group were reported as having a significant ability to differentiate MIA/preinvasive lesions from IACs (15,16). Recently, as a state-of-the-art analytical method, a deep-learning technique has also been adopted to differentiate IACs from MIA/preinvasive lesions. Multiple studies have shown that a deep-learning algorithm was superior both to radiologists and to a size-based logistic regression model for this specific task (17,18). However, several important questions still remain unanswered, and future research should be conducted to address the following questions: Which would be better between deep-learning technique and 3D measurements including mass for differentiating

IACs from MIA/preinvasive lesions? Will adding clinical characteristics to an image-based deep-learning algorithm provide additional value? How exactly can radiologists differentiate IACs from MIA/preinvasive lesions with the assistance of a deep-learning algorithm? We are cautiously expecting that ever-evolving deep-learning approaches can have a chance to outperform the existing analytic methods, especially when clinical information is added, and ultimately improve radiologists' performance to differentiate IACs from MIA/preinvasive lesions.

In conclusion, the differentiation of IACs from MIA/preinvasive lesions on preoperative CT examinations is clinically relevant and will continue to be investigated with various radiological technologies. It should be stressed that studies using existing techniques should be designed, performed, and interpreted with due consideration of image variability, and research on the latest techniques should be developed through comparisons with existing methods and careful weighing of the advantages and disadvantages of each technique.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1645). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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