

# While size matters—advanced “Radiomics” remain promising for the clinical management of ground glass opacities

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The increasing utilization of diagnostic high-resolution chest CT (HRCT) scans in clinical practice and the implementation of low-dose HRCT lung cancer screening are resulting in the identification of a growing number of incidentally and screen-detected pure ground-glass nodules (pGGN) (1-3). Consequently, the notoriously difficult clinical management of persistent (defined present for  $\geq 3$  months) sub-solid pulmonary nodules including pGGN, represents an increasingly recognized conundrum.

Previous retrospective studies investigating surgically resected, unselected sub-solid nodules (pGGN and part-solid nodules) clearly demonstrated that the majority (50–70%) of these lesions belong to the spectrum of lung adenocarcinoma, ranging from atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) to invasive adenocarcinoma (IA) (4,5). While these histological subtypes have been associated with distinct biological behaviors reflected by post-treatment survival (6,7), data evaluating the natural history of these lesions or studies specifically investigating pGGN remain sparse (8). Nevertheless in compared to IA, post-surgical recurrence and lung cancer related mortality is extremely rare in patients with AAH, AIS and MIA (6,7). These diverse patient outcomes clearly indicate the need to develop personalized treatment strategies for these patients. Therapeutic interventions should be tailored based on the aggressiveness of the lesion and a subgroup of indolent

lesions (AAH, AIS and MIA) may potentially be amenable to active HRCT surveillance. This is particularly important since aggressive surgical resection such as lobectomy is associated with significant procedure-related mortality, morbidity and health-care costs (9). Furthermore these lesions are commonly detected in older individuals with significant comorbidities rendering them at even higher risk of death due to competing causes (10). In other words, although these lesions may never reach clinical significance during the lifetime of a considerable subset of patients, these patients are still at risk for substantial iatrogenic treatment related morbidity and mortality. Unfortunately, while comprehensive histological classification of these lesions correlates well with patient outcomes, the requirement of surgical removal of the entire lesion precludes the opportunity to apply this classification for personalized patient management. Smaller biopsy specimens, such as bronchoscopic or image-guided biopsies, are by definition not suitable for this comprehensive analysis. Therefore alternative means of pre-treatment risk stratification such as blood and imaging-based biomarkers are being explored as valuable alternatives.

Although the recently published 2017 Fleischner Society guidelines provide strong evidence-based guidance for the initial management of pGGN, the recommendations regarding the optimal time for intervention, e.g., surgical resection or stereotactic body irradiation therapy (SBRT),

are largely based on expert opinion (11). Based on these guidelines pGGN <6 mm (average of the long and short axis diameters) generally deserve no further follow-up, while lesions  $\geq 6$  mm should be re-evaluated by HRCT 6 to 12 months later and if unchanged every 24 months thereafter until 5 years of follow-up have been completed (11). Interventions are recommended for pGGN growing >2 mm or developing a solid component (11).

However, several recently published prospective and large cohort studies indicate that sub-solid nodules and more specifically pGGN rarely become clinically relevant (4,8,12). Only 13% of all pGGN enlarged during follow up and 4% of ultimately surgically resected pGGN were classified as IA (4,12). The single patient presenting with a pGGN who eventually developed recurrent lung cancer had a large (27 mm) lesion at the time of diagnosis (4,12). Among all the surgically resected sub-solid nodules all but one cancer represented stage 1A disease, and during 10-year post-resection follow-up only 1.6% (2 cases) recurred (4,12). Most aggressive lesions appear to be characterized by a significant solid component of >2 mm raising the question whether currently recommended management strategies are prematurely triggering surgical interventions in response to a >2 mm size increase of pGGN in the absence of the development of a solid component is resulting in overtreatment (4,8,12). In the opinion of experts and in our own clinical practice surgical interventions, biopsy or SBRT are typically triggered by the emergence of a significant (>2 mm) solid component rather than a simple increase in the size of the ground glass component of the pGGN (4). In addition, we also carefully consider patient preferences and other patient-related factors such as age and comorbidities before deciding whether or not to pursue aggressive interventions versus follow up imaging. This complex decision-making process is currently not standardized and largely based on expert opinions and joint decision-making. Better risk-stratification approaches (both for nodules and patients) including blood and imaging-based biomarkers are urgently needed to ultimately guide surveillance and treatment decision-making for patients with sub-solid pulmonary nodules.

We have successfully developed and validated a new software application, Computer Aided Nodule Analysis and Risk Yield (CANARY), using the distribution of HRCT density-based exemplars for the risk-stratification of pulmonary nodules of the lung adenocarcinoma spectrum. Based on a single pre-treatment HRCT, CANARY is able to reliably quantify tissue invasion, predict post-treatment recurrence free survival and classify lesions as indolent (AIS/MIA)

versus aggressive (IA). We have also developed and validated a CANARY-based risk stratification approach to classify patients with pulmonary lung adenocarcinoma into three distinct prognostic groups based on a single time point HRCT (13,14). Nevertheless, the optimal biomarker allowing longitudinal risk monitoring and providing treatment decision support throughout active radiological surveillance, remains elusive and is subject to ongoing research.

In a recently published single-institution retrospective case series of 63 patients with pGGN [2005–2015], Heidinger and colleagues provide additional information on the radiological assessment of sub-solid pulmonary nodules (15). The investigators report the radiological-pathological correlation of simple size, shape, semi-automated volume and average density measurements with the histological classification and invasiveness of a subset of surgically resected sub-solid pulmonary nodules, specifically pGGN (15). In their clinical cohort of consecutive patients with surgically resected lung adenocarcinomas, pGGN represented approximately 12% of all cases (15). Nodule volume and average density were measured in a semi-automated fashion by a single investigator using the open source image processing application OsiriX while nodule diameter and roundness (ratio of long and short axis) were based on linear measurements by two radiologists (15). Radiological variables were correlated to histological consensus classification and the number and size of the invasive foci (15). The study confirmed that the majority of pGGN represent histologically indolent lesions (53 cases were not IA, 84%) (15). Analyzing the immediate pre-operative CT (average 1 month prior to surgery) the authors observed statistically significant correlations between linear size measurements and lesion volumes with histopathological invasion (15). In contrast, there was no statistically significant correlation between nodule roundness and average nodule density with histopathological invasion (15). Consequently, the authors conclude that two-dimensional measurements of the lesion diameter are currently sufficient for the clinical risk-stratification of pGGN and that the more sophisticated volumetric approaches and density-based texture analysis tools used in their study do not add any additional value at this time (15).

While this conclusion may apply to currently available clinical techniques, which are largely restricted to two-dimensional linear measurements, it is important to highlight several limitations regarding these conclusions.

First, given the study design and the current clinical

guidelines none of the included pGGN are <6 mm in size and therefore no conclusion about the radiological assessment of small pGGN can be drawn.

Also, while the average lesion diameter increases between AIS, MIA and IA, there is considerable overlap in nodule size, severely limiting the clinical applicability of these linear measurements for risk stratification.

In addition, despite the authors' conclusion that intra- and inter-observer variability for these size measurements are acceptable, it is important to point out that their data further support the previously observed inter and intra-observer variability of  $\pm 2$  mm. This degree of variability is potentially clinically significant and can limit the clinical implications of these measurements. In contrast, the authors do not report the inter- and intra-observer variability for their volumetric measurements. It is well established that the performance of volumetric measurements is highly dependent on the employed techniques. Using different types of volumetric techniques other investigators have previously shown volumetric measurements to be superior to linear measurements and therefore further studies regarding the value of alternative volumetric measurement techniques are warranted (11,16).

Furthermore, given the known heterogeneity of these lesions, the observed lack of correlation between average radiological and histopathological invasion is not surprising. As highlighted above using a more sophisticated texture analysis approach (CANARY) we successfully characterize solid and sub-solid pulmonary nodules of the lung adenocarcinoma spectrum. Interestingly, in a separate recently published manuscript, Nemeč and colleagues reported that the distribution of CANARY based texture exemplars correlated to histopathological tissue invasion in the same dataset of patients with pGGN. This further highlights the value of more sophisticated texture analysis tools for the risk-stratification of these lesions (17).

Lastly, while the authors emphasize that invasive foci can be observed in pGGN <10 mm, they do not correlate their data to clinically relevant survival outcomes.

In summary, the clinical management of incidentally and screen-detected pGGN represents an emerging clinical challenge. Although histopathological risk stratification correlates to clinically relevant patient outcomes the need for surgical biopsy precludes its clinical use to guide the management of pGGN. While clinically available linear size measurements provide some clinical value, intra- and inter-observer variability and overlap between cases with different levels of invasiveness restrict their applicability. In contrast,

volumetric texture based classification approaches such as CANARY appear to be very promising, but additional data characterizing the longitudinal evolution of these lesions in relationship to clinically relevant patient outcomes and the determination of intervention thresholds is needed.

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### Footnote

*Conflict of Interest:* All authors and Mayo Clinic have a financial interest in the CANARY technology used in this research and have received royalties less than the federal threshold for significant financial interest in the preceding 12 months from licensing the technology to IMBIO.

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