

GGO and minimally invasive adenocarcinomas: how to deal with?

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In this issue of the Journal, Mai *et al.* report on the development of a model that predicts the malignancy and invasiveness of ground-glass nodules (GGNs) based on CT-scan features (1). Similar to previously reported studies, the proposed model showed random forests could achieve 95% and 83% accuracy to predict malignancy and invasiveness, respectively. GGNs may actually corresponds to multiple histopathological entities from the World Health Organization, including atypical adenomatous hyperplasia, adenocarcinoma in situ, as well as minimally-invasive adenocarcinoma, defined as a GGN up to 3 cm with up to 5 mm invasion; the later possibly being mucinous and/or non-mucinous (2). From a radiological standpoint, pure GGN have to be distinguished at computed-tomography (CT)-scan, from sub-solid and part solid-solid nodules, that may combine limited to more extensive solid component, that is more frequent in larger lesions, and is significantly associated with invasion (3,4).

From a clinical standpoint, a major challenge is to weight the radiological features, the risk of evolution and invasiveness of the lesion over time, to ensure an accurate decision-making at the individual patient level. GGN may actually present with various evolution patterns (5): (I) regression of the nodule, which is actually rare; (II) stable size, which is the most frequent pattern, observed in more than 70% of cases; (III) increase in size of the ground-glass areas, which may be regular or not, but usually with prolonged doubling time—what is observed in 10% of the patients; appearance of a solid component, which may reflect invasive adenocarcinoma, occurring in 8–12% of patients. A major question is the duration of the follow-up to assess those patterns. The size of the GGN is then an

important predictor, as lesions of 10 mm or more may have a more rapid evolution (6).

From a practical standpoint, the first step is then discussion of differential diagnoses between benign and tumoral—including pretumoral—lesions; indeed, more than 50% of GGNs may actually correspond to benign lesions, and only a minority of GGN corresponds to invasive adenocarcinoma (3). In this setting, the second step is follow-up; the recent Fleischner Society update include the management of GGN: for pure GGN, size cut-off to repeat CT-scan is 6 mm, with a time interval of 6 months minimum for the first imaging, and then a 2-year delay (7).

With regards to invasive tools to characterize GGNs, 18-fluorodesoxyglucose positron emission imaging is limited as GGNs usually not show hypermetabolism, even if at risk of progression to invasive adenocarcinoma (8). CT-scan guided transthoracic needle biopsy may be associated with good diagnostic sensitivity, but actually depends on the size of the lesion and the presence of solid component (9). Circulating-free DNA analysis for oncogenic mutations associated with lung adenocarcinoma may be a tool that still requires validation in the setting of making the diagnosis of malignancy and assessing the risk of invasiveness (10).

In this setting, the results of the study presented in this issue of the Journal validate previous findings and recent recommendations from the Fleischner Society also adapted by the National Comprehensive Cancer Network guidelines (11). Ultimately, whenever GGNs are surgically resected, a major prognostic tool may be the consolidation over tumor ratio in the setting of subsolid nodules, that is significantly correlated with survival (12). Clinical trials are being conducted in Japan, with stratification on this consolidation

over tumor ratio. In this setting, minimally-invasive surgery and sub-lobar resection should be considered.

To conclude, a key message regarding the management of GGNs is the need for multidisciplinary discussion, with a clear trend towards less aggressive management, prolonged follow-up, before any decision is taken for surgical resection or stereotactic radiotherapy. Partnership with patients is one key in this setting, where less is actually better.

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Footnote

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