The search for reliable markers of ground glass opacity prognosis: The truth remains largely unknown

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Central Message

Novel efforts to combine radiologic, histologic, and genetic data may bring us closer to reliably prognosticating ground glass opacities, but many unknown factors regarding these lesions remain.

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In recent years, significant attention has been directed toward the radiographic entity of ground glass opacities (GGOs), with regard to their malignant potential and attempts to identify risk of aggressive behavior.¹⁻⁷ Previous investigators have demonstrated that histologic subtype significantly affects prognosis, with micropapillary and solid lesions associated with worse outcomes.^{1,2} In addition, a number of authors have attempted to correlate radiographic features with behavior of ground glass lesions.^{4,6,7} No previous studies, however, have simultaneously attempted to link the combination of imaging characteristics, pathologic subtype, and gene mutation in GGOs. This endeavor was uniquely explored in the article by Sun and colleagues⁶ in this issue of the *Journal*.

In this quite timely publication, Sun and colleagues⁶ present their correlative studies linking selected imaging and histologic characteristics, as well as gene mutations associated with adenocarcinomas arising in GGOs. For this study, patients were divided into 2 groups based on tumor appearance on computed tomography, with Group 1 tumors <2 cm and predominantly ground glass, while Group 2 tumors were larger in size and predominantly solid. Upon comparing pathologic subtype and gene mutations between groups, Sun and colleagues⁶ found a number of important results that aid us in our understanding of adenocarcinomas arising from GGOs. Aggressive histologic subtypes (micropapillary and solid) were almost entirely found in group 2. In addition, endothelial growth factor receptor (EGFR) mutations were also significantly more likely in group 2. These findings should, of course, be taken in context; while micropapillary and solid histologic features and EGFR mutations were more common in group 2 than in group 1, they still only represented a minority of patients in group 2. Therefore, it's not as simple as dividing patients into prognostic categories of "high risk" and "low risk;" rather, we can recognize that there are a number of relevant predictors of biologic behavior, but future studies are certainly in need

to be able to provide reliable estimates of outcome on a patient-by-patient basis. Overall patterns identified in this study are worth recognizing, as they may prove helpful in determining the ways that we counsel and treat asymptomatic patients with radiographic evidence of larger, predominantly solid GGOs.

In terms of radiographic characteristics, this investigation accounted for only size and solid component; notably absent from the study were such features as pleural tag, air bronchograms, and lobulation, which have been assessed by a number of previous authors.^{3,7,8} However, this limitation should be deemed a wise choice, rather than an error of omission: in these previous studies, extensive evaluation provided mixed results of questionable utility. Moreover, recent investigations have further shown neither pleural tags, spiculation, nor lobulation to remain relevant after adjusting for the size of the solid component, indicating that those radiographic features are not as important as previously believed.⁴ Thus, it's clear that ongoing studies are critical to identify reliable markers associated with favorable tumor biology, and the innovative approach of Sun and colleagues will hopefully guide us as we aim to gauge prognosis and determine optimal treatment strategy.

With regard to extent of treatment, Sun and colleagues⁶ suggest that their findings may be useful for selecting patients who may benefit from lesser operative procedures,

stating in the perspective statement that “GGOs with a diameter less than 20 mm and a solid component less than 50% are more appropriate for sublobar resection than those with a diameter over 20 mm and a solid component over 50%.” Again, though, a word of caution is in order: extent of resection was not evaluated in this study’s methodology, and additional investigations designed to answer the question of lobectomy versus sublobar resection would certainly be helpful. We are still in our infancy of understanding GGOs, however, and just as it is important to understand how much lung to remove, we are also in need of understanding which GGOs will be adequately managed with alternative modalities (such as ablation or stereotactic radiation), which will require systemic treatment, and which will require no treatment at all.⁹

References

1. Amin MB, Tamboli P, Merchant SH, Ordóñez NG, Ro J, Ayala AG, et al. Micropapillary component in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. *Am J Surg Pathol*. 2002;26:358-64.
2. Cha MJ, Lee HY, Lee KS, Jeong JY, Han J, Shim YM, et al. Micropapillary and solid subtypes of invasive lung adenocarcinoma: clinical predictors of histopathology and outcome. *J Thorac Cardiovasc Surg*. 2014;147:921-8.e2.
3. Moon Y, Sung SW, Lee KY, Sim SB, Park JK. Pure ground-glass opacity on chest computed tomography: predictive factors for invasive adenocarcinoma. *J Thorac Dis*. 2016;8:1561-70.
4. Nelson DB, Godoy MCB, Benveniste MF, Shewale JB, Spicer JD, Mitchell KG, et al. Clinicoradiographic predictors of aggressive biology in lung cancer with ground glass components. *Ann Thorac Surg*. March 10, 2018 [Epub ahead of print].
5. Shewale JB, Nelson DB, Rice DC, Sepesi B, Hofstetter WL, Mehran RJ, et al. Natural history of ground glass lesions among patients with previous lung cancer. *Ann Thorac Surg*. February 9, 2018 [Epub ahead of print].
6. Sun F, Xi J, Zhan C, et al. Ground glass opacities: imaging, pathology, and gene mutations. *J Thorac Cardiovasc Surg*. 2018;156:808-13.
7. Takashima S, Maruyama Y, Hasegawa M, Yamada T, Honda T, Kadoya M, et al. Prognostic significance of high-resolution CT findings in small peripheral adenocarcinoma of the lung: a retrospective study on 64 patients. *Lung Cancer*. 2002;36:289-95.
8. Honda T, Kondo T, Murakami S, Saito H, Oshita F, Ito H, et al. Radiographic and pathological analysis of small lung adenocarcinoma using the new IASLC classification. *Clin Radiol*. 2013;68:e21-6.
9. Antonoff MB. Multifocal lung cancer within ground glass lesions: are favorable outcomes consequent to surgical resection or inherent to the disease? *J Thorac Cardiovasc Surg*. 2018;155:361-2.