Editorial Commentary

Pure ground-glass opacity of the lung: making the case for a lasting cure

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The management of ground-glass opacities (GGOs) is a topic of debate and active investigation. Guidelines suggest computed tomography follow-up for some and tissue sampling including resection for others, depending on identifiable risk factors (1). This treatment paradigm is based on the understanding that pure GGOs frequently comprise premalignant adenomatous lesions, adenocarcinoma *in situ*, or minimally invasive carcinomas and thus have the potential to progress to a higher-grade invasive adenocarcinoma.

In this issue of the journal, Li *et al.* (2) provide an elegant long-term follow-up for patients who had resection for pure GGOs at Fudan University in Shanghai, China. Their analysis suggests that for the 308 patients in their cohort with pure GGOs, 10-year recurrence-free survival is 100% and the risk of developing a second primary lung cancer is 2.4%. Surgical pathology of the GGOs was quite revealing: adenocarcinoma *in situ* in 38%, minimally invasive adenocarcinoma in 40%, and invasive adenocarcinoma in 22%. It is important to note that these were all pure GGOs without solid component on imaging, with measured diameters of 11.8±5.0 mm. All were treated with surgery. There was no difference in outcomes when comparing sublobar resection and lobectomy; about 60% had sublobar resection, mostly wedges.

There are several key questions when considering treatment of pure GGOs in the context of this study. First, how would the oncologic outcomes differ if a surveillance strategy is chosen compared to a surgical approach? The natural history of pure GGOs was investigated by Kakinuma *et al.* who demonstrated in a Japanese prospective study of 795 patients with 1,229 GGOs of which 1,046 were pure GGOs that the mean time to progression to part-solid nodules was 3.8±2.0 years (3). Out of 35 patients who underwent resection for pure GGOs in this study, it was interesting to note the pathologic findings: 14% atypical adenomatous hyperplasia, 60% adenocarcinoma *in situ*, and 26% were minimally invasive adenocarcinoma; no invasive adenocarcinomas were found in this group. In contrast, the pathologic findings of 49 part-solid nodules consisted of 2% atypical adenomatous hyperplasia, 20% adenocarcinoma *in situ*, 53% minimally invasive adenocarcinoma, and 24% invasive adenocarcinoma.

Second, the modality by which pure GGOs are treated

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is certainly of interest. Specifically, how would stereotactic radiation or other ablative techniques compare to the excellent long-term surgical outcomes presented here? Particularly for nodules with a minimal risk of having spread to regional lymph nodes and where the risk of under-staging is reasonably low, the question of surgical intervention versus ablation would need to be addressed. Early investigations show some evidence to the efficacy of these alternative approaches (4,5), though they would need to be measured against the gold-standard of surgical resection and studied as rigorously as done by Li *et al.* The other consideration here is the high rate of EGFR mutation in the present cohort, which highlights the importance of pathologic diagnosis. In the case of small GGOs, this is best done surgically.

The final question relates to the generalizability of the findings by Li *et al.* to non-Asian cohorts. In this study, 73.4% of patients were female and 87% were never smokers—significantly different characteristics than those typically seen in Western lung cancer cohorts which show more uniform gender distribution and with greater history of smoking. In addition, in Li *et al.*'s study, EGFR mutation was seen in the majority of GGOs tested, potentially different from the molecular characteristics of GGOs in non-Asian cohorts. We refer the reader to an excellent review on molecular pathology of GGOs written by an international collaborative group (6). The question of generalizability remains and certainly warrants further attention and interdisciplinary discussion of individual patients.

Clearly, we need more long-term data like those presented by Li *et al.* to identify which GGOs require surgical resection and which can be watched. This becomes even more important in the patient with multiple GGOs. We look forward to some answers from the ongoing Thoracic Surgery Oncology Group (TSOG) registry for patients with multifocal GGOs (7).

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