Editorial Commentary

Pure ground-glass opacities (GGO) lung adenocarcinoma: surgical resection is curative

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The promise of low-dose computed tomography (LDCT) scanning and the resulting stage-shift for non-small cell lung cancer (NSCLC) has also presented the challenge of how to manage smaller lesions, especially those that are pure ground glass opacities (GGO) (1,2). It has been previously established that pure GGO lung adenocarcinoma has an excellent 5-year recurrence-free survival (RFS) of 100% after undergoing surgical resection (3,4). However, the indolent nature of pure GGO lung adenocarcinoma necessitates longer term outcomes to properly judge the true overall and recurrence-free survival rates. The recent article by Li *et al.* (5) "Ten-year follow-up results of pure GGO-featured lung adenocarcinomas after surgery" aims to provide clarity on just this topic.

Li and colleagues enrolled 308 patients at a single center in China who underwent surgery during a 6-year period from 2007 to 2013. Using high-resolution computed tomography (CT), the investigators defined GGO as a hazy opacity with the presence of underlying pulmonary vessels or bronchial structures. Additionally, the authors further stratified the lesions as pure GGO—defined as having a consolidation/tumor ratio (CTR) =0, mixed GGO—defined as having a CTR <1, or solid nodule with a CTR equal to 1. The importance of this distinction is demonstrated in significantly worse 5-year RFS for mixed GGO (87.6%) and solid nodules (73.2%) (3). The authors also collected data regarding rates of secondary primary lung cancer (SPLC). 73.4% of their cohort were female, the majority were non-smokers (87%), and the average age was 55.9 (range, 27–76) years. These demographics are important to consider, as the tumor biology may be significantly different in those who are never-smokers (6), and female gender is an independent, favorable, prognostic factor (7). The average tumor diameter was 11.8±5.0 mm on CT and 10.0±4.6 mm on pathology. 60.8% underwent sublobar resection and 39.2% underwent lobectomy. There was no recurrence in any of the patients who underwent sublobar resection or lobectomy 10 years after surgery. In addition, there was no difference in overall survival (OS) or SPLC rates between the two groups.

While not the primary focus of their study, Li *et al.* discuss excellent RFS and OS regardless of pure GGO lung adenocarcinoma or mixed GGO. However, this distinction is particularly important when considering previous studies that have revealed increased incidence of recurrence after resection in patients with mixed GGO lung adenocarcinoma (8-11). Because of this, the authors make the case that pure GGO lung adenocarcinomas should be treated as a distinct entity from mixed GGO lung adenocarcinomas. Given the excellent RFS in the patients undergoing sublobar resection in this population, the authors also advocate for timely resection to prevent the progression of the lesion such that a lobectomy will be required. They further advocate for timely resection to prevent the development of a solid component that will make the lesion a mixed GGO lung adenocarcinoma that no longer has a 100% RFS.

The authors also demonstrate a change in the type of operation performed, with 100% of resections being via lobectomy at the beginning of the study, and only around 25% undergoing lobectomy by the end of the study. Since the randomized clinical trial conducted by the Lung Cancer Study Group in 1995 established lobectomy as the standard of care in early-stage lung cancer (12), there have been numerous contemporaneous studies that demonstrate non-inferiority of sublobar resection. Suzuki *et al.* demonstrated that in GGO-dominant lung cancer (defined as CTR ≤0.25) with maximum tumor diameter ≤2.0 cm sublobar resection achieved a 99.7% 5-year RFS with no incidences of local recurrence (13). Similar results were shown even in the solid nodule population. Altorki *et al.* enrolled 697 patients with tumor size ≤2.0 cm (excluding patients with pure GGO lesions) in a randomized controlled trial that showed non-inferiority of sublobar resection compared to lobectomy in terms of 5-year disease-free survival (DFS) (63.6% *vs.* 64.1%) and 5-year OS (80.3% *vs.* 78.9%) (14). Saji *et al.* similarly enrolled 1,106 patients with tumor size ≤2.0 cm and CTR >0.5 and demonstrated non-inferiority of sublobar resection compared to lobectomy in terms of 5-year DFS (88.0% *vs.* 87.9%) and 5-year OS (94.3% *vs.* 91.1%) (15). The difference in these results compared with the results of the Lung Cancer Study Group trial have largely been attributed to improvements in imaging and staging over the last two decades.

It is important to note that most of the patients in this study would have fallen under the criteria of tumor size ≤2.0 cm as the average tumor diameter was 1.18 cm. The increasing trend toward sublobar resection towards the latter part of the study matches the authors' recommendation that sublobar resection be the resection of choice in this population. This is also in line with the other studies demonstrating that sublobar resection is at least non-inferior to lobectomy in the tumor size ≤2.0 cm population, and may indeed be superior. Saji *et al.* demonstrated a slight survival benefit of sublobar resection as above which was attributed to higher pulmonary reserve in the setting of SPLC or other malignancies. However, it should be noted that the study by Saji *et al.* demonstrated a median reduction in forced expiratory volume in 1 s (FEV_1) at 6 and 12 months for sublobar resection of 10.4% and 8.5%, respectively compared to a median reduction in FEV_1 at 6 and 12 months for lobectomy at 13.1% and 12.0% respectively (P<0.0001 for both) (15). This reached statistical significance but did not reach the pre-trial cut-off of an improvement of 10% in reduction of FEV_1 for clinical significance. Similarly, in the Altorki study, the reduction in FEV_1 at 6 months was 4% for sublobar resection and 6% for lobectomy with confidence intervals that did not overlap (14). Though this seems to be a statistically significant difference, it does not represent a clinically significant difference. The 10-year SPLC rate in this study was 2.4% which is lower than the reported rate of 10-year SPLC rate of 8.36% reported by Han *et al.* for all lung cancer patients (16). Therefore, despite lower rates of SPLC with pure GGO lung adenocarcinoma compared to other lung cancers, there still are instances of SPLC that require long term surveillance and preservation of lung volume is of interest. Theoretically, when the recurrence rates are low, preservation of lung volume is of particular interest to increase pulmonary reserve and allow further treatment options for SPLC and other malignancies in the long term.

This study did have limitations, primarily related to the single-center, retrospective nature of the study. As previously noted, the demographics may not reflect the typical population of patients with NSCLC, raising questions about the generalizability of this data to the larger lung cancer population world-wide. Further, as typical in retrospective analysis, it is unclear which selection criteria were used to enroll these patients in the study. Given variability in assessing CTR by different radiologists, there could be classification bias where a lesion may be misdiagnosed as mixed GGO or vice versa. In addition, though overall demographic data was provided there was no specific demographic data regarding the groups between those undergoing sublobar resection or lobectomy. Therefore, there could be potential confounding variables that are not accounted for that affect the analysis of RFS and OS in the two groups.

Nevertheless, this study presents important 10-year results after surgical resection of pure GGO lung adenocarcinoma. The excellent 10-year RFS and 10-year OS in this patient population suggest that surgical resection can be regarded as a cure which is very rare in the invasive lung cancer population and further highlights the remarkable results of this study.

The authors make a convincing case that pure GGO lung adenocarcinoma should be differentiated from other forms of lung cancer and that sublobar resection in a timely manner should be the standard of care for this form of lung cancer. Such measures may allow more patients to be treated by allowing more patients to be surgical candidates and may lead to increased preservation of pulmonary reserve. Preservation of pulmonary reserve is particularly

interesting in this population given the especially young age in this group which could portend a survival benefit at even longer-term follow-up.

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Footnote

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