



## Surveillance of ground glass nodules—when is enough, enough?

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Lee *et al.* provide important information about the long-term behavior of ground glass nodules (GGNs) (1). They carried out a retrospective review of 208 GGNs, detected during routine health check-up CT scans (1–3 mm slice thickness), that were stable for 5 years (78% pure GGNs) (1). Growth was defined as an increase in the largest total dimension of  $\geq 2$  mm (others have shown high inter- and intra-observer variability for changes of  $< 2$  mm) or the development of a new solid component (presumably visible on mediastinal windows although not explicitly stated). Of the 208 initially stable GGNs, 27 (13%) subsequently grew (12% of pure GGNs and 17% of part solid GGNs). The median amount of growth was 3.2 mm after a median period of 8.6 years (from the first scan). Only one GGN grew substantially (from about 8 to 28 mm) over 10 years, but it is unclear if this was a pure GGN or whether or how it was treated. Development of a new solid component was seen in 16% of the 208 GGNs. There was a clear association between growth and development of a new solid component, but growth sometimes preceded or followed development of the solid component, or there was no growth.

The subsequent outcomes are less clearly reported. It appears that only 3 patients underwent resection (1 adenocarcinoma *in situ*, 1 Minimally invasive adenocarcinoma, and 1 invasive adenocarcinoma). There were no deaths among any of the 208 patients and no recurrences (in these 3 patients). The conclusion of the study was that continued surveillance of GGNs is warranted, even if stable for 5 years (1).

It is well established that not all GGNs progress—in fact the majority do not even over 10 years of observation.

There is evidence that genetic features of GGNs that progress and that remain stable differ (2). Lee *et al.* also report that the majority of GGNs detected on routine screening were stable, although a specific percentage cannot be calculated from this study that only briefly describes the initial catchment cohort from which the study population (GGNs that were stable for 5 years) is drawn (3).

The study appears to be written with a binary mindset of cancer *vs.* benign—i.e., a small subset of GGNs turned out to be lung cancer, and lung cancer is uniformly a potentially fatal disease. I think this is an incorrect concept. There is ample data that the vast majority of (persistent) GGNs are histologically in the adenocarcinoma spectrum (precancerous, preinvasive or invasive adenocarcinoma). To me, the question is not whether a persistent GGN is malignant, but how will it behave. Because GGNs that are invasive cancer exhibit indolent behavior (4), one must balance the rate of progression of such lung cancers against a patient's projected life expectancy in deciding whether to treat it at all. Indeed, a median rate of progression of 3 mm over 8.6 years as reported by Lee *et al.* is hardly alarming. However, Lee *et al.* apparently agree, because it appears that a decision to treat was made in only 3 of the 27 GGNs that showed growth after 5 years (1).

Lee *et al.* do not provide guidance regarding criteria for intervention (1). In my current algorithm, it is the development of a new solid component or growth of a solid component of  $> 2$  mm on mediastinal windows of a thin slice CT—usually with several scans showing steady (subtle) progression. Similar criteria have been shown in long-term prospective studies to avoid intervention in

most patients without compromise to those eventually undergoing resection (all had stage I cancers with no subsequent recurrences) (5). In addition, we need to move from a static to a dynamic view with ground glass/lepidic adenocarcinoma (6,7). The rate of progression must be balanced against the rate of progression of comorbidities and the patient's life expectancy.

This study by Lee *et al.* is useful in defining the duration of surveillance, as some have suggested that subsequent follow-up is unnecessary if GGNs are stable for 3 years (1). Others have also shown that a minority of initially stable GGNs eventually progress (6). Nevertheless, given the rate of progression and of intervention, the degree of benefit in preserving health is small (8). One of the initially stable GGNs in the study by Lee *et al.* grew substantially. I think it is justified to continue to follow initially stable GGNs beyond 5 years. However, it may be reasonable to scan every 2–3 years, and we should also be careful not to overreact when changes are small or the rate of change is very protracted.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The authors is accountable for all aspects of the work in ensuring that questions related

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