

Ground Glass Nodules: Just the Beginning

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We have entered an era of lung cancer screening, to the extent that low-dose CT scans for lung cancer screening are being offered for free at some institutions (<http://www.lahey.org/lungscreening/>). Although free may be a very good price, it may come at substantial cost. These costs include a wide range of detected abnormalities, many of which have uncertain clinical significance and can create considerable anxiety in patients and their health care providers. One of these abnormalities is the ground glass nodule (GGN), a focal CT finding where there is increased attenuation through which normal parenchymal and airway structures remain visible. In the current issue of the journal, Kobayyashi et al.¹ describe their experience in observing GGNs. Their aim was to describe the natural history of a most unnatural phenomenon, a radiographic finding in asymptomatic individuals. They followed 108 lesions in 61 individuals detected at screening or as incidental findings. Most of the findings remained stable with observation up to 12 years. Twenty-seven percent increased in size, with some showing both growth and increases in a solid component. In their analysis, all lesions demonstrating growth did so within the first 3 years. Primarily on the basis of growth, 21 patients went on to surgical resection with almost half the lesions being atypical adenomatous hyperplasia or adenocarcinoma-in-situ, with most of the remaining lesions being minimally invasive adenocarcinoma. They correctly conclude and suggest that GGNs should be observed for at least 3 years before deciding that they will remain stable. Before incorporating this into practice, there is still much to consider. For example, the context is very important. The population Kobayyashi studied is a uniquely Japanese population. Two-thirds of the subjects were nonsmoking women, and 90% of the adenocarcinomas contained epidermal growth factor receptor mutations. Although indolent growth may be a nearly universal characteristic of GGNs, the “natural” history needs to be defined in other populations as well.

This study does not answer some of the most important questions surrounding GGNs. With wide spread CT screening for lung cancer, GGNs will become more frequent, and the goals of management will become more complex. Minimizing procedures, radiation exposure, and expenditures will become increasingly important. An emphasis on outcomes, with less focus on specific histology and when and how to intervene will be needed. Kobayyashi et al. had universally good outcomes, but with significant costs, including 12 pulmonary resections for premalignant lesions (adenomatous hyperplasia and adenocarcinoma-in-situ). Given the very indolent nature of all of these abnormalities, some of the malignant lesions might be candidates for “overdiagnosis” of lung cancer. To this end, several organizations have considered the GGN and developed guidelines and recommendations. This includes the National Comprehensive Cancer Network, the American Association for Thoracic Surgery, and most recently the Fleischner Society.² Of these, the Fleischner Society recommendations are the most complete and complex.

In 2005, the Fleischner Society published their ubiquitous guidelines for small pulmonary nodules incidentally detected on CT scan.³ These recommendations are simple, clear, and easily condensed into the small table that is posted next to radiology workstations around the world. However, in 2005, they only dealt with solid nodules. Now the Fleischner

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Society has moved on to subsolid pulmonary nodules, and things get much more complex. GGNs are more heterogeneous, in their radiographic appearance, behavior, and histology. As expected, the new guidelines are much more complex than those for solid nodules and unlikely to be condensed into a single, simple table. All the recommendations made are well researched and justified by current literature and available data, but still represent the opinions of experts in the field. They have yet to be tested prospectively and have not been applied in the real world. Research has shown that even the simple guidelines for solid nodules can be difficult to follow.⁴ This fact may represent one of the issues the Fleischner GGN recommendations will have to face in the real world: Are physicians willing and able to follow a complex nodule follow-up pathway, and are the descriptors (size, density, cystic component, etc.) distinct enough to be applicable in daily practice? The current data are robust for pure GGNs between 5 and 8 mm and justify a more conservative approach for this subtype. It gets more complicated once mixed solid and GGNs are to be assessed. The clear distinction between solid and ground glass as well as the size and proportion of each component determines outcome and follow-up recommendations. Interpretative consistency will be very important in such cases.

There are technical issues raised by the Fleischner Society GGN recommendations. The Fleischner society recommends contiguous 1-mm thick slices for assessment of GGNs, something not addressed in other guidelines. There are potential pitfalls with respect to differences in reconstruction algorithms, which may alter the appearance and hence

density of a GGNs and the challenges of comparing scans from two different institutions and/or manufacturers should not be overlooked.

These recent recommendations from the Fleischner society on the management of GGNs provide a solid foundation and starting point for further investigation. They touch on many areas of uncertainty and acknowledge the limitations of many of our standard procedures, such as positron emission tomography scans and biopsies, and they place an emphasis on minimizing radiation exposure and procedures. Their approach is supported by the new data from Kobayashi et al. in this issue of the journal. It is hoped that these recommendations will guide practitioners and more importantly serve as the foundation for outcome-oriented investigation in the management of these increasingly ubiquitous radiographic findings.

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