CHEST

Achieving Clarity About Lung Cancer and Opacities

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Management of patients with ground-glass nodules (GGNs) is a common clinical issue. Retrospective surgical series demonstrate that these are primarily lepidic predominant adenocarcinomas, minimally invasive adenocarcinoma, and adenocarcinoma in situ.[1,2] Although many studies suggest that these cancers have a less aggressive behavior,[3,4] we lack good management protocols.

The article by Sawada et al[5] in this issue of *CHEST* represents a major advance in the management of GGNs. It is a long-term study: 226 patients accrued from 2000 to 2005, with a follow-up period of 10 to 15 years. Included patients had a GGN $\leq$ 3 cm in maximal diameter, with or without an area of consolidation (dense area on lung windows). Approximately 25% had multiple GGNs and approximately 25% had a partly consolidated GGN. A standard protocol for observation was used (essentially annual CT for pure GGNs and every 6 months for partly consolidated GGNs). Progression was defined as growth of the overall maximum diameter (in 35%) or a new or increased consolidated component (in 65%). Few pure GGNs progressed, and < 1% progressed during later follow-up (Fig 1). A minority of partly consolidated GGNs progressed (all within 3 years). Furthermore, among resected lesions, only 4% of those that began as a pure GGN were identified as invasive adenocarcinoma, whereas increasing proportions of those that began as a partly consolidated GGN were invasive adenocarcinomas. Among 124 resected cancers, 99.2% were stage IA. With a postresection follow-up of almost 10 years, only 1.6% recurred. Note that 73% of resected lesions did not progress but were resected because of patient preference (or occasionally the physician's preference), consistent with the greater uncertainty about the nature of GGNs in 2000 to 2005.

FOR RELATED ARTICLE SEE PAGE 308

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The primary message of this long-term study is that observation of GGNs is appropriate: very few pure GGNs progressed, and almost none were invasive cancers. Even among partly consolidated lesions, the majority did not progress. Moreover, 99% of resected cancers were stage IA, and long-term survival was excellent. Two lung cancer deaths occurred (one in a pure GGN); however, three times as many patients died of unrelated causes. Furthermore, although there was no perioperative mortality, one can speculate that perhaps further observation might have been appropriate in some of the resected nonprogressing (pure) GGNs.

The paper by Sawada et al[5] corroborates other studies demonstrating that the solid/invasive component is the major determinant of prognosis.[4,6-8] In the eighth edition of the TNM stage classification, only the solid portion (clinical stage) or the invasive portion (pathologic stage) determines the T category.[9]

However, criteria to define a solid component are unclear (eg, lung/mediastinal windows, slice thickness). A recent large prospective study by Kakinuma et al[10] provides some guidance, distinguishing pure GGN, heterogeneous GGN (partly consolidated on lung windows), and partly solid GGN (with a mediastinal window solid component). Additionally, a heterogeneous or solid component was required to be $\geq$ 2 mm, because there is major interobserver and intraobserver variability at < 2 mm.[11,12] Kakinuma et al[10] found that all the invasive adenocarcinomas had a partly solid appearance ($\geq$ 2 mm). However, a solid component $\geq$ 2 mm developed in only 6% of pure GGNs and 22% of partly consolidated (heterogeneous) GGNs at 5 years. Moreover, of the 1,253 GGNs,

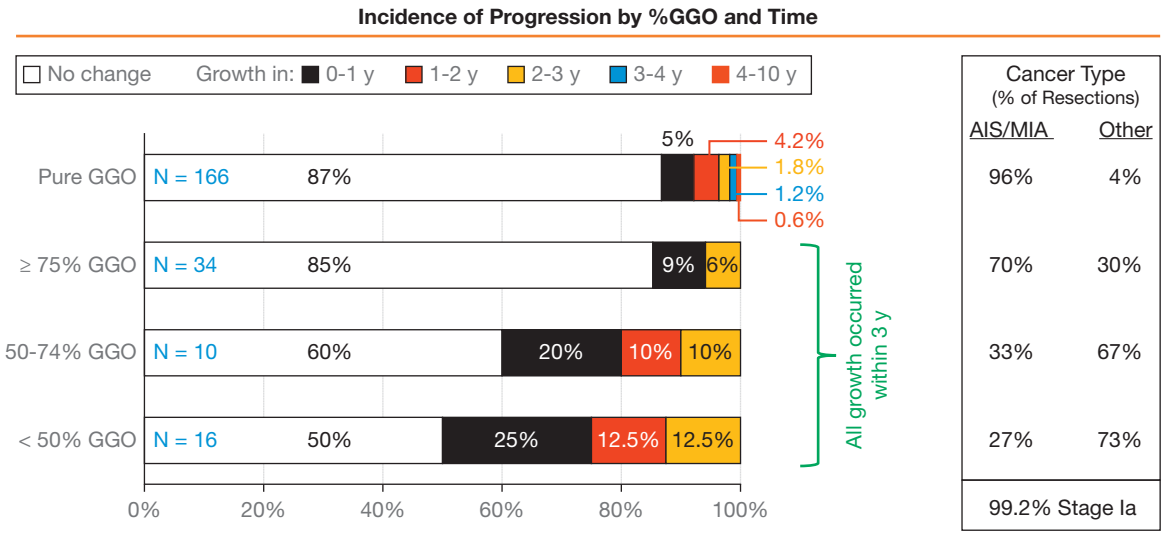

Figure 1 – *Outcomes by time interval and type of ground-glass nodule during long-term follow-up of 226 patients. AIS = adenocarcinoma in situ; MIA = minimally invasive adenocarcinoma. (Data taken from Sawada et al.[5])*

only 1% were eventually found to be invasive adenocarcinoma, and 98% of resected cancers were stage IA (2% stage IB). Thus, this prospective multicenter study suggests it is safe to wait until a mediastinal window solid component ≥ 2 mm develops.[10]

Although both the Sawada et al[5] and Kakinuma et al[10] papers suggest that observation is frequently appropriate, how this should be done is vague. Sawada et al suggest that annual CT scanning of partly consolidated GGNs might be stopped after 3 years but continued indefinitely for pure GGNs; this seems counterintuitive given the chance of it becoming an invasive cancer. Kakinuma et al suggest annual CT scanning of pure GGNs and scanning every 6 months for heterogeneous or partly solid GGNs (without addressing duration).

The long-term, prospective, and large-cohort nature of the Sawada et al[5] and Kakinuma et al[10] studies provides good evidence toward defining criteria for intervention for a GGN. In addition, in my opinion, we need to start factoring in the rate of change. A gradual 2-mm increase in size over a period of 5 years may not be an appropriate trigger for resection. My personal criteria for intervention of a GGN are listed in Table 1; these must be considered together with patient factors (eg, age, major comorbidities, and patient values and preferences).

There is intense anticipation that molecular characterization will predict biological behavior. Although molecular fingerprinting undoubtedly yields important new insights, things are always more complicated that initially thought, and much research and follow-up is needed to generate the necessary data. The study by Sawada et al[5] suggests that we should just look at what is already in front of our eyes: the radiographic features of GGNs are highly predictive of biological behavior. It will be hard to do better than this.

TABLE 1] A General Management Plan for GGNs

GGN Type	Follow-Up Schedule	Triggers for Intervention[a]
Pure GGN	LDCT every 12 mo	Maximum dimension > 3 cm[b] New solid area ≥ 2 mm on MW ≥ 25% growth/y[b]
Heterogeneous GGN	CT every 6 mo × 2 y; if stable revert to LDCT every 12 mo	Maximum dimension > 3 cm[b] New solid area ≥ 2 mm on MW ≥ 25% growth/y[b] (of total or solid area)
Partly solid (2-5 mm solid portion on MW)	CT every 3 mo × 1 y; if stable revert to CT every 6 mo	Maximum dimension > 3 cm[b] Growth of solid area by ≥ 2 mm on MW ≥ 25% growth/y[b] (of total or solid area)

CT should be performed with 1.25-mm slice thickness. GGNs = ground-glass nodules; LDCT = low-dose CT; LW = lung window; MW = mediastinal window.
[a]Assuming no doubt about measurement (generally requires ≥ 2 interval scans).
[b]Speculative recommendation, based on limited data.

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