

# What do we know about ground-glass opacity nodules in the lung?

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**Abstract:** Ground-glass opacity nodules (GGNs) in the lung attract clinical attention owing to their increasing incidence, unique natural course, and association with lung adenocarcinoma. A long and indolent course of a GGN makes it difficult to manage. Current extensive clinical, radiological, pathological, and genetic studies on GGNs have shed light on their pathogenesis and allowed development of a reliable strategy of management. The present editorial provides answers to clinical questions related to GGNs, such as the natural course, follow-up, prediction of growth, and resection techniques. Finally, I discuss the etiology of GGNs, which has not been fully elucidated so far.

**Keywords:** Ground-glass opacity nodules (GGNs); growth; epidermal growth factor receptor (EGFR); lung adenocarcinoma

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The introduction of low-dose chest computed tomography (CT) screening into the clinical practice has led to an increase in the detection rates of lung nodules. A considerable percentage of these nodules are ground-glass opacity nodules (GGNs). The characteristics of patients with GGNs are different from those of patients with typical lung cancer. Patients with GGNs are usually women, nonsmokers, of Asian origin, and relatively young. Most of the papers on GGNs are from Asian countries, especially Japan and Korea. The management of a GGN is particularly important because its long and indolent course requires frequent CT screening, which may cause high radiation exposure, economic burden, and psychological stress to patients.

As a clinician who has encountered a considerable number of patients with GGNs, I would like to discuss several issues that are clinically important in the management of these patients.

(I) Most clinicians have probably observed that a percentage of GGNs disappear spontaneously (a transient GGN). My research group found that 37% of pure GGNs (pGGNs) and 48% of mixed GGNs (mGGNs) regressed or disappeared within

3 months, which suggested their inflammatory nature (1).

(II) What is the natural course of a persistent GGN? In an actual clinical setting, most GGNs seem to remain unchanged for a long time. Many doctors tend to neglect the clinical importance of GGNs and often report that small GGNs have little clinical significance just like micronodules in the thyroid. Several papers reported long-term follow-up results of patients with GGNs. Hiramatsu *et al.* (2) first reported that 26% of GGNs significantly increased in diameter (over 2 mm of the whole GGN). Matsuguma *et al.* (3) and Kobayashi *et al.* (4) reported that 41% and 29% of mGGNs, respectively, showed significant growth. Two similar Korean studies were also reported. Chang *et al.* reported that 12% of pGGNs increased significantly (5). My group also reported that 26% of GGNs showed a significant increase and that mGGNs, initial large size, and old age were independent risk factors for growth (6). I believe that the proportions of GGNs that increase in size are higher than most doctors expect.

(III) How long shall we follow up GGNs? Kobayashi *et al.* (4) analyzed 108 GGNs and found that all GGNs showing a significant increase in size grew within 3 years. Therefore, they recommended that patients with GGNs should be followed by clinicians for at least 3 years. I agree that 3 years is the minimum duration of follow-up in these patients. Although it is uncommon to find a GGN grow after long-term standstill, my group revealed that 2 of 90 GGNs (2.2%) followed up for more than 4 years showed significant growth after 4 years (6). Personally, I recommend increasing the interval of CT screening from 1 to 2 or 3 years for a GGN, which does not change during the initial 3-year follow-up.

(IV) Can we predict GGNs that will grow eventually? A considerable proportion of GGNs disappear spontaneously. An ill-defined border of a GGN may be a sign of spontaneous regression, which suggests an inflammatory nature (1,7). Several characteristics of GGNs may be the sign of future growth and malignancy. Initial large size, spiculated border, the presence of bubble lucency, and a history of cancer are generally accepted risk factors for growth and malignant transformation of GGNs. Kobayashi *et al.* (8) analyzed 120 GGNs with the ground glass opacity portion over 50% (solid portion of less than 50%). Large initial size and smoking history were associated with growth. My group also revealed that an initial size over 10 mm, the presence of the solid portion, age over 65 years, and male sex were risk factors for an increase in size (6).

Recently, Kobayashi *et al.* (9) investigated the differences in genetic features of lung adenocarcinoma presenting with GGN with and without growth. They analyzed the mutation or rearrangement of epidermal growth factor receptor (EGFR), K-ras, anaplastic lymphoma kinase (ALK), and HER2 from 104 resected GGNs and analyzed the genetic differences according to the growth status. The EGFR mutation was the most common (64%), followed by K-ras (4%), HER2 (4%), and ALK (3%). The remaining 26 GGNs showed no genetic difference (quadruple negative). Among 104 GGNs, a follow-up thin-section CT was performed in 71 lesions, 30 of which showed growth. Among the remaining 41 GGNs, five

lesions were classified as a no-growth group because they were followed up for more than 2 years. Among 25 quadruple-negative GGNs, only 5 were evaluated for growth and one GGN was shown to increase in size. However, among 39 GGNs with the EGFR mutation, 28 GGNs were evaluated for growth and 27 were shown to increase in size. They concluded that EGFR-driven GGNs showed a tendency for growth and quadruple-negative GGNs were associated with no growth. This finding is clinically significant because it shows that the presence of the EGFR mutation, known as driver oncogene of a GGN, is a strong indicator of GGN growth and an indication for surgical resection.

Although Kobayashi *et al.* (9) reported a very important finding, two points have to be mentioned. First, a substantial number of GGNs were not included in the growth analysis because the follow-up period lasted less than 2 years. In particular, only 5 of 26 quadruple-negative GGNs were analyzed. Although the difference was statistically significant, too many data were missing. Second, a genetic analysis of GGNs can be done after surgical resection, and it is difficult to analyze the genetic features of GGNs before surgery. The tissue of a GGN may be obtained using percutaneous transthoracic needle biopsy (PCNB) (10); however, surgical resection without preoperative biopsy is the major strategy in the management of GGNs with high diagnostic accuracy.

(V) When do we recommend surgical resection of a GGN to a patient? Widely recommended indications for biopsy or surgical resection by Fleischner Society include (i) a pGGN of over 15 mm in diameter and (ii) mGGN with a solid portion of 5 mm or more (11). In my opinion, a significant increase in size (over 2 mm) or the appearance of a solid portion may be an indication for resection (12).

(VI) Is it necessary to perform biopsy before resection? I recommend surgical resection rather than needle biopsy because of the following reasons: (i) a high correlation between a CT finding and pathological finding has been established, such as the correlation of microinvasion in pathology and solid portion of a GGN (13,14); (ii) PCNB may cause some procedure-related complications and

takes a long time exposing the performer to high radiation; and (iii) most importantly, introduction of video-assisted thoracoscopic surgery made it easy to remove a GGN without considerable damage to patients. At my institute, we perform resection without PCNB for a GGN if it meets the criteria by Fleischner Society or significant increase in size, and we have reported that 95% of the resected GGNs were malignant (12).

(VII) What is the suitable type of resection for GGNs? Lobectomy is the surgical modality of choice for lung cancer. However, we might ask the question of whether it is necessary to resect one lobe for the resection of a GGN of 10 to 20 mm in size. Many institutes performed limited (sublobar) resection such as segmentectomy or wide-wedge resection for GGNs and reported similar results to those obtained with standard lobectomy (15). Limited resection is preferred to lobectomy because it saves pulmonary function (16). However, lobectomy is still indicated for GGNs with over 25% of the solid portion (15).

(VIII) Another important issue related to GGNs is multiplicity. Roughly, one-third of patients with a GGN have more than two GGNs simultaneously or one after another. According to the current staging system, if two or more malignant nodules are found in the same lobe, it would be T3 and if in a different lobe, it would be T4. Furthermore, if nodules were in a different lung, it would be M1a. This staging system would be correct if we consider that all multiple GGNs were metastatic nodules. Usually, multiple GGNs are all similar in size and are found in different lobes or lungs. My group analyzed the genetic features (EGFR and K-ras) of multiple GGNs resected from the same patients. The analysis of the EGFR mutation showed that high frequency of discordant EGFR mutations (17 of 24, 70.8%) could discriminate tumor clonality (18 of 24, 75%) of multiple lung neoplastic nodules presenting as GGNs (17). Therefore, multiple GGNs seem to be multifocal in origin rather than being intrapulmonary metastasis.

This finding could provide a rationale for the current strategy of surgical resection of dominant GGNs in patients with multiple GGNs (18,19).

(IX) The final question related to GGNs concerns the

etiology. There are several differences between lung cancer with a GGN and typical lung cancer. A GGN is not associated with smoking unlike smoking-related lung cancer. GGNs occur at a relatively young age. Moreover, they develop in the peripheral portion of the lung and many of them show a multifocal origin. Some researchers suggested cooking fumes as a causative agent; however, there is no clear evidence to support this hypothesis. Recently, a multicenter epidemiological study of nonsmoker lung cancer has been launched in Korea. I strongly believe that it will help elucidate the etiology of a GGN.

In conclusion, a GGN is a unique type of lung cancer or a precancerous lesion characterized by a long and indolent course. Regular follow-up and the determination of the type of surgical resection are particularly important because a considerable proportion of GGNs progress into invasive adenocarcinomas, usually driven by the EGFR mutation. Understanding the etiology of GGNs would help prevent their formation and would allow us to develop novel management strategies.

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