Patients are increasingly being identified with a ground-glass lesion on a chest computed tomography (CT) scan. It is not clear whether this is because of an increased incidence, increased awareness (ie, recognition of an abnormality as opposed to considering it an inconsequential finding), or increased identification because of an increasing prevalence of CT imaging. Whatever the reason, how to approach these patients is an issue that increasingly confronts clinicians. This article reviews the available data and proposes management recommendations for these patients.

A ground-glass opacity (GGO) is defined as a hazy increased lung opacity (on CT) with preservation of bronchial and vascular markings. However, this definition requires clarification because such densities are seen in many different contexts. This article discusses abnormalities that are seen in the absence of another disease process, such as a pneumonia (including a viral pneumonia) or interstitial lung disease. It discusses only persistent (not transient) GGOs, and excludes diffuse GGO throughout the lung, or infiltrates that are geographic and not focal (these are generally associated with an underlying disease process). This article is concerned only about a focal GGO in patients who are middle aged or older. Although a GGO may have a solid component, this article primarily focuses on the approach to a pure GGO, or lesion with a solid component but that is still more than 50% GGO. These are usually found incidentally on a CT scan (and generally not visible on a chest radiograph). Examples of GGOs according to the Suzuki classification are shown in Fig. 1. This article addresses only types 1 to 4 in this classification.

This article discusses the range of possible entities, whether there are identifiable risk factors or characteristics that help make a presumptive clinical diagnosis, how often and for how long these should be observed, when and how a biopsy should be done, how these lesions should be treated (ie, lobectomy, segmentectomy, wedge resection, stereotactic body radiotherapy [SBRT], or radiofrequency ablation [RFA]), and how multifocal GGOs should be approached.

**PATHOLOGIC ENTITIES**

A GGO that is not related to another pulmonary or systemic process is most likely to be either a nonspecific benign process or an entity in the adenocarcinoma (AC) spectrum. These entities are predominantly characterized by growth at least in part along preexisting alveolar structures. This pattern of growth is also known as lepidic growth (named after butterflies, Order Lepidoptera, alighting on a branch but not disturbing it). The entities currently recognized in this spectrum include atypical adenomatous hyperplasia (AAH; defined as a lesion <0.5 cm, with mild to moderate nuclear atypia, without stromal invasion), AC in situ (AIS; <3 cm, with moderate to severe nuclear atypia, without stromal invasion), minimally invasive AC (stromal invasion present but overall tumor size <3 cm with <0.5 cm of invasion), lepidic pattern AC (extent of invasion >0.5 cm but predominantly lepidic pattern of growth), and...
conventional acinar and papillary AC with minor lepidic growth around the periphery of the tumor. The key concept in this progression is the presence and relative extent of invasion. Historically (since the 1999 World Health Organization [WHO] classification), the presence of invasion has separated AAH and bronchioloalveolar carcinoma (BAC) from invasive AC, but the extent of invasion was not a key criterion. A critical supporting concept is that the entire tumor needs to be examined (not just a biopsy) to pathologically exclude invasion. Thus any reported series of BAC based on biopsy only is inappropriately classified. Similarly, multicentric tumors or pneumonic tumors commonly show noninvasive components on biopsy despite obvious radiologic evidence for invasion. Widespread lack of awareness of the need to examine the entire (resected) tumor to appropriately classify these tumors has led to the recommendation to abandon the term BAC; however, the concept of complete assessment also applies to the new terminology (AAH, AIS, AC). These entities are discussed further in the article by Travis elsewhere in this issue.

In most cases, stromal invasion leads to dense scarring that is apparent as a solid density radiographically. This dense scar is the basis of the Suzuki system described earlier. The exceptions are that of papillary and micropapillary AC, which are recent additions to the spectrum of pulmonary AC. In some cases, the papillary AC component had been confused with the BAC pattern, which is a consideration in analysis of the existing literature. The significance is that papillary ACs are believed to have a similar prognosis as conventional invasive ACs, whereas micropapillary ACs are generally considered to have a worse prognosis. Most lung ACs are mixtures of different patterns, thus pure papillary or micropapillary ACs are rare.

If AAH and AIS are considered precursor lesions to more aggressive, invasive AC, there should be similar but increased genetic complexity in the invasive portion of the AC component in comparison with the noninvasive portion of the same tumor. This prediction has been shown to be true in at least some tumors. AAH clearly has a lower level of complexity than AIS, but the rate of progression of AAH and AIS to more clinically significant lesions is hard to estimate. Specifically, because AAH is generally an incidental finding in a lobe resected for another purpose, it is not possible to estimate its rate of progression.

**APPROACH TO MANAGEMENT**

**Clinical Diagnosis**

The first step in approaching a patient is to make a presumptive clinical diagnosis, along with an
estimate of how reliable this is. The risk of malignant disease, namely AC in situ and invasive AC, must be estimated. The best treatment of AIS is debatable, but there is no substantial experience with observation as a strategy, and a diagnosis of AIS is assumed to be an indication for treatment.

Among GGOs that were resected, most were AIS or AC (Fig. 2A, B). The rate of AC is increased if there is a solid component. Because all of these patients were resected, these data probably do not apply to all patients with a GGO, of whom many are believed to be more appropriately observed, presumably because their risk of cancer is believed to be low.

The influence of size in pure and semisolid GGOs is shown in Fig. 3A, B among studies involving a period of follow-up (or biopsy). For pure GGO that are less than or equal to 10 mm in size, the chance of invasive AC seems to be minimal, although there is about a 25% chance of AIS. Pure GGOs greater than 10 mm in size have a higher risk of AIS (~40%) and a small risk of AC (~20%). The presence of a solid portion seems to be more significant; even if the lesion is less than or equal to 10 mm, about 50% have AIS and about 25% have AC. Most semisolid lesions greater than 10 mm have AIS or AC. However, the number of studies is limited, and the data in part come from a skewed patient population in which the suspicion of malignancy was high enough to justify surgical removal of the lesion.

There are few data regarding other patient or lesion characteristics that can influence the risk of cancer. There is some evidence that GGOs have little relationship to smoking,8,9 although this has not been clearly addressed. Whether a prior history of lung cancer affects the incidence of malignancy in a GGO is unclear.10,11 Other factors, such as age or geographic location, have not been studied. All the studies to date have come from Asia, with 1 exception.12

**Observation: When and How?**

This article focuses on GGOs that are persistent, but being exact about this definition is difficult. No standard criteria have been established, but we propose that the lesion appears unchanged during a period of approximately 2 to 3 months. CT screening shows that about 30% of GGOs on baseline scan disappear after 2 months, as do about 50% of new GGO lesions detected on repeat screening evaluations.13 Most of the GGO lesions that disappear are believed to be related to infection. In particular, lesions with radiographic features that suggest infection (ie, lesions that are less focal, often with borders that fade gradually and with a more irregular shape) should be treated with antibiotics and a follow-up scan to show that they have resolved. Data show that most (~95%) lesions that disappear do so within the first 3 months.14,15

What happens in time to a persistent GGO? Data from several studies are shown in Fig. 4. The length of follow-up ranged from 9 to 40 months. The reported outcomes vary, probably because the patients included, and the nature of the endpoints and follow-up, have varied. Most lesions either remained the same or decreased in size. About 10% to 20% increased in size, although the proportion was higher (~50%) in 2 studies.16,17 One of these studies16 only reported on patients who were selected for resection; no reason is apparent why

![Fig. 2. Findings at resection of a GGO. Distribution of diagnoses of resected lesions for (A) pure GGO and (B) semisolid GGO lesions. AAH, atypical adenomatous hyperplasia; Adeno, adenocarcinoma; AIS, adenocarcinoma in situ; F/U mo, follow-up period (in months); N pts, number of patients. (Part (A) Data from Refs.15,26,44,46,73–75; and (B) Data from Refs.12,15,26,46,59,60,74–77)](image-url)
the incidence of an increase in size was so high in
the other. The incidence of development of a solid
component seems to be low. Whether the lesion is
a pure GGO or semisolid seems to have little influ-
ence in predicting subsequent changes, but the
data are limited.

A study of 125 GGOs (after documented stability
for 3 months) found that, by multivariate analysis,
the initial lesion size, and perhaps a prior history
of lung cancer, were the only factors affecting the
risk of growth over time. The risk of growth at 5
years was 66% for lesions greater than 10 mm
versus 14% if less than or equal to 10 mm initially.

There was no sign of a plateau that could support
termination of follow-up after a certain point.

It is difficult to measure a GGO. The difference
between the lesion and the underlying lung is
subtle, often the borders are indistinct, and the
lesion may change in size with breathing. Even for
the more usual (ie, solid) CI tumors, data show
false-positive and false-negative (FN) assessments
of growth of 10% to 50%, using different mea-
surement methods (maximal length, diameter,
volume), and poor interobserver and intraob-
server consistency for size differences of less
than 1.5 to 2 mm. Volumetric programs that

![Fig. 3. Diagnosis according to size. Diagnosis according to size for (A) pure GGO and (B) semisolid GGO. AAH, atypical adenomatous hyperplasia; Adeno, adenocarcinoma; AIS, adenocarcinoma in situ; F/U mo, follow-up period (in months); N pts, number of patients; NSCLC, non–small cell lung carcinoma. (Part (A) Data from Refs. 17,46,58,60,78; and (B) Data from Refs. 46,59,75)](Image)

![Fig. 4. Outcomes during observation. Outcomes of GGO lesions after a period of observation. BAC, bronchioloalveolar carcinoma; F/U mo, follow-up period (in months); N pts, number of patients. (Data from Refs. 10,15–17,57,60,79)](Image)
work well with solid lesions do not seem to function with GGOs, although recent programs show intraobserver and interobserver differences for volume measurements of approximately plus or minus 15% to 20% for GGOs greater than or equal to 8 mm and plus or minus 30% to 40% if less than 8 mm.

In addition, a decrease in size cannot be taken as an indication that a lesion is benign. Several studies observed a decrease in size during an observation period in approximately 20% (range 14%–25%) of resected ACs that appeared as a GGO. This may be a select group, because they were chosen for resection despite the decrease in size. A decrease in size may be associated with the development of a solid component (but not always). There is also a suggestion that a period of decrease in size may be an expected occurrence during the progression of a GGO into an invasive cancer.

The traditional approach of putting a great deal of importance on the growth of a lesion is problematic. Studies of screening CT have shown that the growth rate of malignant nodules is often not as consistent as expected. The difficulty in determining the size of a lesion seems to account for only part of this variation.

Among lesions that were observed, approximately 5% were eventually found to be AC, and approximately 10% to 30% were AIS (Fig. 5). The incidence of AC may be slightly higher in patients with semisolid lesions or in patients with a history of non–small cell lung carcinoma (NSCLC). The rest of the lesions were either benign or are still being followed. It is possible that some of the followed lesions are malignancies (ie, indolent). It is also likely that a proportion of the lesions still being followed would be diagnosed as AAH if they were biopsied.

A significant amount of data show that, on average, cancers arising from GGO lesions exhibit slow rates of growth (volume doubling times [VDT] of ~500 and ~750 days for semisolid and pure GGO lesions). Among pure GGO lesions, 50% to 90% of patients have tumors with a VDT of greater than 400 days, and this was greater than 800 days in 20% to 50%. For semisolid lesions, about 50% have a VDT of greater than 400 days, but, in at least 1 study, a small proportion has a short VDT of less than 100 days. These data come from studies involving CT screening, which may be skewed toward more indolent tumors. Furthermore, some variability exists in the growth patterns observed among GGO lesions that were followed and eventually shown to be NSCLC.

Given the variability of results and limited number of studies, an initial interval between scans of 6 months for pure GGO and 3 months for a semisolid lesion seems reasonable. If stability is shown, subsequently increasing the interval to 12 and 6 months, respectively, seems to be justified.

Confirmatory Tests

Positron emission tomography (PET) imaging has no usefulness for GGO lesions. A study of

![Fig. 5. Diagnoses during observation. Diagnoses made during observation. AAH, atypical adenomatous hyperplasia; Adeno, adenocarcinoma; AIS, adenocarcinoma in situ; F/U mo, follow-up period (in months); N pts, number of patients. (Data from Refs. 10, 15–17, 57, 60, 73, 79)
GGOs 1 to 3 cm in size reported a sensitivity of 10% and a FN rate of 90%.33 For lesions that have a solid component, the usefulness of PET is limited because of the size. The amount of PET uptake decreases almost linearly for solid lesions less than 2 cm; particularly for lesions less than 10 mm, the sensitivity is low and the FN rate is high.33–35

Methods of biopsy include bronchoscopic biopsy, transthoracic needle, or surgical (excisional) biopsy, typically via video-assisted thoracic surgery (VATS). Bronchoscopy for peripheral lesions has a low yield (~30%),36 and a GGO that cannot be visualized with fluoroscopy is even more difficult. Electromagnetic navigation can guide a biopsy, but confirmation of being in the right place (ie, with peripheral ultrasound) may not be possible. No data have been reported regarding the yield of such techniques specifically for GGO lesions.

Specific potential issues with CT-guided transthoracic needle biopsy include that GGO lesions are small and, by definition, not very cellular, and bleeding can obscure the lesion and make a second pass difficult. The sensitivity has been reported to be about 50% to 90%, but, with inclusion of indeterminate results, it is about 50% to 75%.37–39 The sensitivity is slightly worse in smaller lesions (35%–67% for lesions ≤10 mm vs 75%–80% for lesions >15–20 mm).37,39 The sensitivity also seems slightly worse for pure GGO lesions than for lesions that are greater than 50% GGO (50% vs 80%).38 CT fluoroscopy may yield slightly better results.39

However, the real issue is the FN rate, but this is not well defined. The FN rate has been reported to be about 20% to 30%, but the length of follow-up has been short and not well defined (and some negative biopsies that were subsequently overturned by repeat biopsies were not counted as negative).38,39 Furthermore, the rate of concordance between the needle biopsy (ie, AAH, AIS of AC) and the resection diagnosis is approximately 70%.38

A VATS excisional biopsy of a GGO requires preoperative CT-guided localization, because these lesions are almost never palpable. Many different methods of marking have been used, including technetium, blue dye, hook wires, injection of lipiodol or barium with intraoperative fluoroscopy. The choice of method is guided by local experience and preference.40–42 VATS excisional biopsy is accomplished reliably and with minimal morbidity.42

Treatment

The data showing slow average growth rates of malignant GGO lesions prompt the question of whether a less aggressive treatment than lobectomy is warranted. One way to assess this is to examine the incidence of nodal involvement among resected malignant GGOs (Table 1). The incidence of nodal involvement seems to be consistently low for lesions that are greater than 50% GGO, with only 1 exception.43 This study was not limited to patients who were at clinical stage I; it is possible that inclusion of patients who were at cII and cIIIA accounted for the high incidence of nodal involvement. However, for cII GGO lesions of less than 2 cm, the surrogate endpoint of nodal involvement suggests that sublobar resection may be reasonable. These results are true even for GGO lesions that were classified as invasive cancer.

Outcomes of patients with greater than 50% GGO tumors who underwent primarily sublobar resection are consistently excellent, as shown in Table 2. This finding is true for both retrospective analyses as well as prospective studies.44–48 It is not possible to compare lobectomy, segmentectomy, and wedge resection in these studies, but there does not seem to be any trend toward worse outcomes in studies with a large proportion of wedge resections. However, overall and disease-free survival may not be optimal endpoints in this case (because patients may survive despite recurrence of an indolent tumor, unrelated deaths with no evidence of recurrence are counted as an event, and new primary lung cancers are counted as an event). The best treatment outcome measure is recurrence, which is uniformly zero after sublobar resection. Again, these excellent results for GGO lesions are true even for tumors that were classified as invasive cancer.

However, caution should be used in applying the results in Table 2 prospectively. These results were all from patients who were selected for sublobar resection, and the criteria by which they were selected are often not fully defined. In at least some of the studies, careful attention was paid to the distance to the margin, sometimes with sophisticated intraoperative assessment, or a frozen section diagnosis of a Noguchi type A or B tumor. Furthermore, all of these studies were performed in Japan. Whether these results can be extrapolated to other countries, to GGO lesions in general, or without strict intraoperative management, is uncertain.

One prospective phase II study has been reported with carefully defined entry criteria and intraoperative management (using a modified stapler; specimen inflation; ≥1 cm margin; only Noguchi type A, B on frozen section; elastin stain; and segmentectomy or lobectomy if there were any concerns).44 Despite the careful intraoperative management of these patients, 3 local recurrences at the staple line were reported in this study.49 The final results of this study have not yet been released.
Some investigators have advocated limited resection of AIS (ie, BAC), noting that, in general, a GGO lesion is more likely to be AIS. These investigators reported 94% to 100% reliability of a frozen section to correctly diagnose AIS. These data are from studies that used sophisticated and stringent criteria for how the frozen section was performed; applying this more broadly may not yield the same result.

The lack of nodal involvement with a GGO is in contrast with that for solid cl lesions, for which several studies have shown that, even for solid nodules less than or equal to 1 cm, there is a worrisome incidence of nodal involvement (average 22%, range 7%–54%).

**MANAGEMENT OF MULTIFOCAL GGO**

A particular problem is how to manage patients with multiple GGOs, which we call multifocal disease. It is probably best not to think of this mechanistically as hematogenous (or aerogenous) dissemination, but as a manifestation of cancer development at multiple sites (ie, field cancerization and multiple primary tumors), given consistent survival results that are dramatically different than other forms of distant dissemination (even to solitary sites, with 23% 1-year survival in the staging revision database). Multiple (vs single) GGOs do not seem to be more ominous for risk of invasive cancer, either in general or with a dominant lesion that is AIS or AC.

During a median follow-up period of 46 months, new lesions developed in 26% in a study of 27 patients with 91 GGOs. All new lesions were pure GGOs of less than 10 mm (most were simply observed and not resected because they showed no signs of being invasive cancers). No new lesions were noted in...
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Inclusion criteria: studies involving mostly sublobar resection of >50% GGO lesions.

Abbreviations: DFS, disease free survival; n, number of patients undergoing sublobar resection; OS, overall survival.

a Prospective study.

b Data for whole cohort; not for a specific subgroup.

c Data reported per lesion (150 GGO lesions in 27 multifocal patients).

d New primary cancers were counted as a recurrence.

e By tumor disappearance ratio (between lung and mediastinal windows).

f Two-year survival.
another study of 58 patients (14 with multiple GGOs) with a median follow-up of 24 months.61

Thus the management of patients with multiple GGOs should be determined primarily by the size of the lesion and the presence of a solid component. The management is not different for multiple lesions; the nature of the lesions themselves does not seem to be changed if there are many or only 1.

SUMMARY OF MANAGEMENT RECOMMENDATIONS

Lesions that appear inflammatory in nature (eg, irregular, nonfocal, indistinct borders) should undergo a follow-up CT scan in 6 to 12 weeks. Antibiotics can be given if there is a strong suspicion of a bacterial infection. A lesion that is persistent with little change after 3 months is unlikely to disappear later, so a definitive management plan should be defined at this time.

A pure GGO less than or equal to 10 mm has approximately a 25% chance of being AIS and less than a 5% chance of being AC; for a pure GGO of greater than 10 mm, the chances of AIS and AC are approximately 40% and 20%. A semisolid (>50%) GGO has approximately a 50% chance of being AIS and a 25% chance of being AC if less than or equal to 10 mm and a 50% chance of being AC if greater than 10 mm.

The documented low rate of growth of pure GGOs less than or equal to 10 mm10 and the typically indolent growth of AIS justify observation of such lesions. It may be reasonable to observe very small semisolid GGO or those with a very small solid component, but this has not been addressed in studies to date. Given the uncertainties of growth rates, initial intervals between scans of 6 months for pure GGO and 3 months for a semisolid lesion seems reasonable. If stability is shown, subsequently increasing the interval to 12 and 6 months, respectively, seems to be justified. The data currently available suggest that follow-up should be continued indefinitely, although perhaps eventually at extended (eg, 2 year) intervals if prolonged stability has already been shown.

The chance of progression of a GGO during observation seems to be about 20% to 30% over several years, although few are eventually found to be AC (most are AIS). The risk seems to be substantial for larger pure GGO lesions (>10 mm) and is also higher for semisolid lesions. A decrease in size does not indicate that further imaging is unnecessary, unless the decrease is dramatic and serially observed in multiple scans. The imprecision of all current methods (including volumetric) must be kept in mind when interpreting small changes in size.18–22 The appearance of a solid component in a lesion is an indication for intervention.

A pure GGO greater than 10 mm or one with a solid component, in general, requires intervention. PET imaging has no role. Some physicians prefer to use a positive result of a needle biopsy to plan therapy, but a negative result warrants further intervention given the FN rates of 20% to 30% reported so far.38,39 A VATS excisional biopsy is definitive, but generally requires some form of preoperative localization.

The data from both retrospective and prospective studies in Asia are consistent that a cT1aN0M0 tumor that is either a pure GGO or greater than 50% GGO can be effectively managed with a sublobar resection. This seems to be true regardless of whether the final histologic diagnosis is AIS or invasive AC.62 However, it has not been shown that these results apply in other parts of the world, and, in general, they have involved careful attention to many details (eg margin status, distance to margin). Sublobar resection can reasonably be recommended for patients with a cT1a greater than 50% GGO lesion of less than 2 cm in the context of a careful preoperatively planned protocol. Although the incidence of node involvement has been low, systematic N1 and N2 node sampling should be done until further data are available. Other forms of local therapy (eg, SBRT or RFA) that lack the histologic confirmation, careful attention to margin status, or invasive nodal staging can only be recommended in the context of a clinical trial.

SUMMARY

The detection of GGO is increasingly common. Sufficient data have been accumulated for recommendations for observation, intervention, and treatment modalities to be made. However, an understanding of many nuances and uncertainties in the available data is needed to avoid making management errors.

REFERENCES


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