Ground-Glass Opacity Lung Nodules in the Era of Lung Cancer CT Screening: Radiology, Pathology, and Clinical Management

Article *in* ONCOLOGY · March 2016

CITATIONS
119

READS
2,359

6 authors, including:

Jesper Holst Pedersen
Rigshospitalet
185 PUBLICATIONS **7,877** CITATIONS
SEE PROFILE

Zaigham Saghir
Copenhagen University Hospital Gentofte
71 PUBLICATIONS **1,847** CITATIONS
SEE PROFILE

Laura Hohwü Thomsen
Copenhagen University Hospital Gentofte
21 PUBLICATIONS **956** CITATIONS
SEE PROFILE

Birgit Skov
Rigshospitalet
64 PUBLICATIONS **3,539** CITATIONS
SEE PROFILE

Ground-Glass Opacity Lung Nodules in the Era of Lung Cancer CT Screening: Radiology, Pathology, and Clinical Management

Jesper Holst Pedersen, DMsci[1], Zaigham Saghir,PhD[2], Mathilde Marie Winkler Wille, PhD[3,4], Laura Hohwu Thomsen,PhD[4], Birgit Guldhammer Skov, DMsci[5], Haseem Ashraf, PhD[4,6]

ABSTRACT: The advent of computed tomography screening for lung cancer will increase the incidence of ground-glass opacity (GGO) nodules detected and referred for diagnostic evaluation and management. GGO nodules remain a diagnostic challenge; therefore, a more systematic approach is necessary to ensure correct diagnosis and optimal management. Here we present the latest advances in the radiologic imaging and pathology of GGO nodules, demonstrating that radiologic features are increasingly predictive of the pathology of GGO nodules. We review the current guidelines from the Fleischner Society, the National Comprehensive Cancer Network, and the British Thoracic Society. In addition, we discuss the management and follow-up of GGO nodules in the light of experience from screening trials. Minimally invasive tissue biopsies and the marking of GGO nodules for surgery are new and rapidly developing fields that will yield improvements in both diagnosis and treatment. The standard-of-care surgical treatment of early lung cancer is still minimally invasive lobectomy with systematic lymph node dissection. However, recent research has shown that some GGO lesions may be treated with sublobar resections; these findings may expand the surgical treatment options available in the future.

Introduction

Low-dose computed tomography (LDCT) is accepted as an effective screening method in high-risk individuals for the purpose of reducing lung cancer mortality. Following the results of the National Lung Screening Trial (NLST) in the United States,[1] LDCT screening for lung cancer is being implemented in the United States and China[2,3] and is under consideration in many other countries. The management of screen-detected nodules, which must include methods for distinguishing between malignant and benign nodules, is crucial to the success of a screening program. Nodules that demonstrate ground-glass opacity (GGO) on CT are particularly challenging on account of their malignant potential and heterogeneous characteristics.[4] This review focuses on the radiologic and pathologic features of GGO nodules, along with the clinical management of these lesions.

A commentary on this article appears on page 275.

Radiological Features of GGO Nodules

GGO nodules are defined radiologically as focal areas of slightly increased CT attenuation through which the normal lung parenchyma structures, airways, and vessels are visually preserved; in fact, airways are often recognized more clearly because of the increased contrast between intraluminal air, which appears very black, and the surrounding abnormal lung parenchyma, which has increased density. Increased lung opacity occurs when the amount of air in the airspaces and in the lumen of the airways decreases and when the soft-tissue structures increase in size and/or amount. Thus, a reduction in the volume of the airspaces as well as a partial or total replacement of the air in the airspaces by cells or fluid will result in increased opacity.[5] In GGO nodules, airspace volume reduction is only

[1]Department of Cardiothoracic Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[2]Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark
[3]Department of Imaging, Nordsjællands Hospital, Hillerød, Denmark
[4]Department of Respiratory Medicine, Gentofte University Hospital, Hellerup, Denmark
[5]Rigshospitalet, Department of Pathology, University of Copenhagen, Copenhagen, Denmark
[6]Akershus University Hospital, Department of Radiology, Lørenskog, Norway

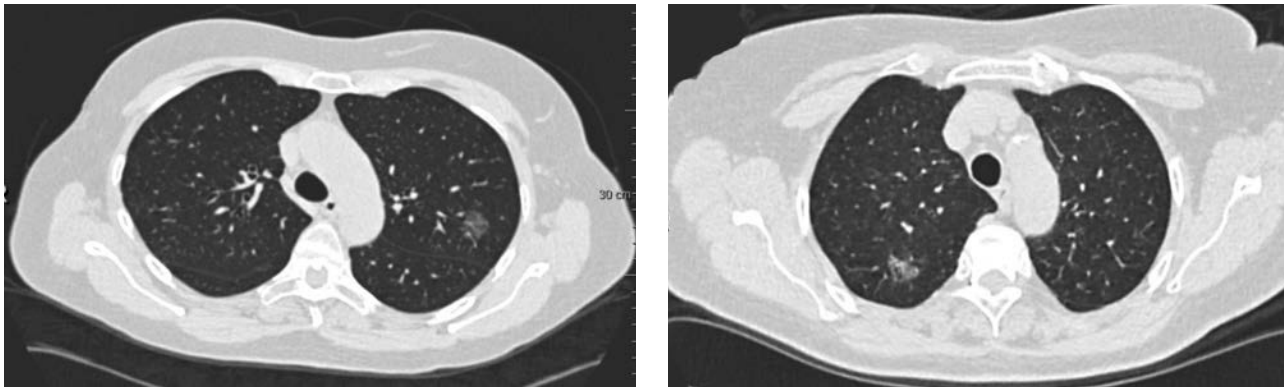

Figure 1. Pure (A) and Part-Solid (B) Ground-Glass Opacity Nodules From Participants in the Danish Lung Cancer Screening Trial. Final diagnosis of both nodules was malignant adenocarcinoma.

partial, and the alveolar lumen is only moderately filled with cells and fluid, to a degree where complete consolidation of the lung parenchyma does not occur.

GGO nodules, also referred to as subsolid nodules, are radiologically divided into two categories: 1) pure GGO nodules, which contain no solid component (Figure 1A), and 2) part-solid GGO nodules, which contain both a pure GGO region and a consolidated region (Figure 1B).[6] These part-solid nodules are also called mixed GGO nodules. In malignant part-solid GGO nodules, the solid part histologically represents invasion, whereas the pure GGO areas are considered adenocarcinoma in situ (AIS). Solid transformation of GGO nodules is thus considered a strong indicator of malignancy.[7] A study showed that, based on the proportion of the solid component, called the consolidation/tumor (C/T) ratio, it may be possible to differentiate between invasive and noninvasive malignant disease.[8] GGO nodules are often slow-growing, and if malignant transformation from carcinoma in situ does occur, the process may take years—which is why longer follow-up time is necessary (see section on management).

It is important to keep in mind that "GGO" is a rather unspecific radiologic feature seen in a number of clinical conditions involving different pathologic processes. GGO on images may represent alveolar changes, but also interstitial changes, with increased cellularity and fluid within the alveolar wall. Apart from malignant disease, which is often a focal finding, GGO changes can represent lung infections (which may be visualized as patchy findings scattered throughout the parenchyma), lung edema with fluid in the interstitium, patchy increased parenchymal perfusion (ie, mosaic perfusion), or interstitial diseases (where GGO can represent disease activity and may precede irreversible changes, including the development of fibrosis).[9] Knowledge of these pathologies, along with a patient history and observation via repeat scans, is therefore necessary in the diagnostic workup of GGO nodules.

Pathology of GGO Nodules

According to the recent World Health Organization (WHO) classification,[10] adenocarcinoma and its precursors are classified into preinvasive lesions (including atypical adenomatous hyperplasia [AAH] and AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma. A detailed review of the pathologies of these three groups is outside the scope of this review.

In general, lung adenocarcinomas are thought to follow a linear multistep progression in which AAH progresses to AIS, which in turn is followed by invasive adenocarcinoma.

AAH is a localized small (less than 5 mm) proliferation of atypical type II pneumocytes and/or Clara cells lining the alveolar walls and respiratory bronchioles. AIS is a small (3 cm or less) solitary adenocarcinoma that demonstrates pure lepidic growth without stromal, vascular, or pleural invasion (Figure 2). The cell type is mostly nonmucinous (but may rarely be mucinous), and nuclear atypia is absent or inconspicuous.

MIA is a small (3 cm or less) solitary adenocarcinoma with a predominantly lepidic pattern and invasion of 5 mm or less at the largest dimension. If any histologic subtype other than lepidic is predominant, it should be regarded—and measured—as the invasive component.[11] However, the measurement of invasion size can be challenging if multiple foci of invasion are present.[12] If there is doubt about the tumor size, correlation with CT should be done. MIA does not invade lymphatics, blood vessels, or the pleura; contains no necrosis; and does not spread through air spaces. The prognosis is excellent for patients who undergo complete resection for AIS and MIA, as 5-year disease-free survival is close to 100%.

AIS and MIA should not be diagnosed in small biopsies or cytology specimens, as the whole tumor must be evaluated in order to rule out invasion for AIS and to measure the size of the whole invasion for MIA. If a noninvasive pattern is present in a small biopsy, it should be referred to as a lepidic growth pattern of

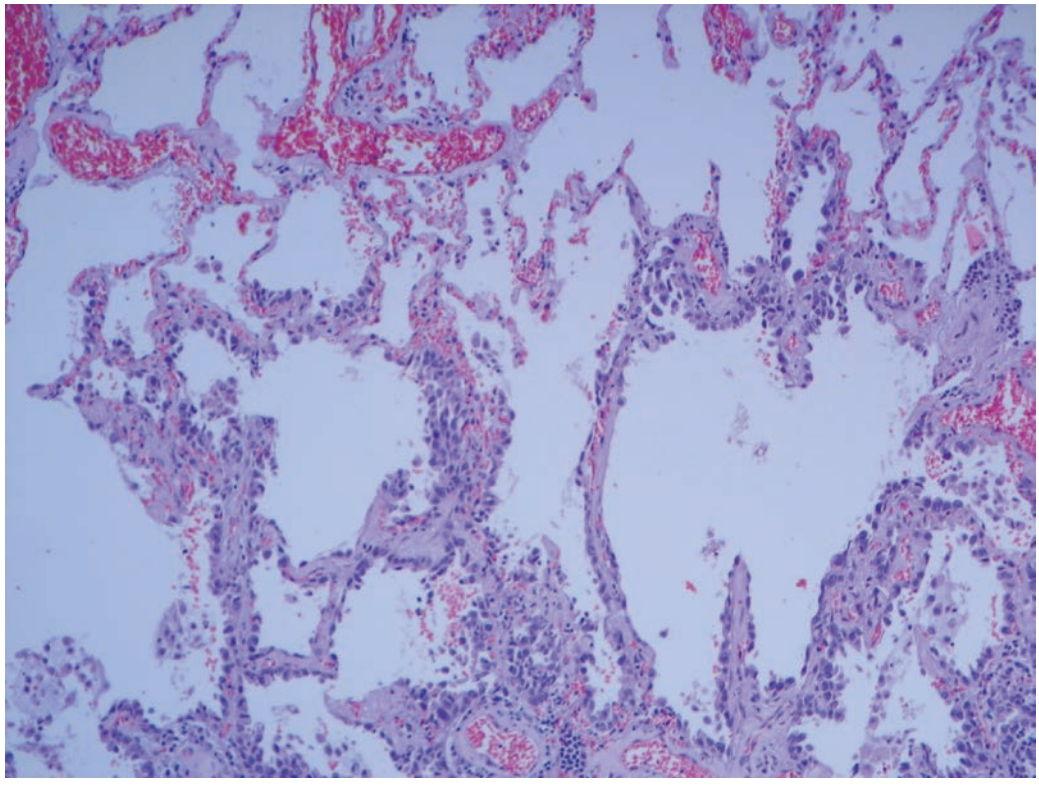

Figure 2. Atypical Adenomatous Hyperplasia With Proliferation of Atypical Type II Pneumocytes Cells Lining the Alveolar Walls.

adenocarcinoma, with a comment added that this could represent AIS, MIA, or invasive adenocarcinoma with a lepidic component.

For tumors with a semisolid pattern on CT, the site for obtaining the biopsy is critical and very important for the final diagnosis. In the peripheral part of the tumor, the biopsy will show a lepidic pattern only, whereas in the more central/solid part, the biopsy may show a lepidic as well as an invasive pattern.

Correlation with CT findings can help determine the most likely final diagnosis. For example, if a biopsy shows a lepidic pattern and CT shows a pure GGO nodule, this would favor a diagnosis of AIS, or possibly MIA, and would make a diagnosis of lepidic-predominant adenocarcinoma less likely, while if a mostly GGO nodule also had a solid component measuring more than 5 mm, this would favor a diagnosis of lepidic-predominant adenocarcinoma.[13-18] However, as mentioned previously, the final diagnosis of AIS or MIA requires a resection specimen, as these entities cannot be diagnosed in small biopsy specimens. It is reasonable to sample possible AIS or MIA lesions and to freeze the tissue samples obtained for possible later use; however, the pathology findings should also be correlated with the CT findings to make sure there are no solid areas suspicious for invasion. If suspicious areas are seen on CT and they are not represented on the histology slides, the frozen samples may need to be processed for histologic examination in order to reach a definitive diagnosis.

Invasive adenocarcinomas are classified into different subtypes according to pattern of growth: lepidic-predominant, papillary-predominant, micropapillary-predominant, acinar-predominant, or solid-predominant. The classification of invasive adenocarcinomas should be determined on the basis of the predominant subtype, with the proportion of all subtypes present measured in 5% increments. This subclassification has prognostic import, since solid and micropapillary adenocarcinomas have a poor prognosis, papillary and acinar adenocarcinomas have an intermediate prognosis, and lepidic adenocarcinomas have a favorable prognosis.[19-21] Invasive mucinous adenocarcinoma with lepidic pattern, formerly classified as mucinous bronchioloalveolar carcinoma (BAC), has been added as another specific subgroup.

The reproducibility of this classification has been evaluated by pathologists.[22,23] In pulmonary adenocarcinomas with classic morphology, there is good reproducibility for the identification of a predominant pattern and fair reproducibility for distinguish-

Address all correspondence to:

Jesper Holst Pedersen, MD, DMsci
Chief Surgeon, Associate Professor
Department of Thoracic Surgery RT 2152
Rigshospitalet
University of Copenhagen
Copenhagen, Denmark
(+45) 35458014
jesper.holst.pedersen@regionh.dk

ing invasive from in-situ patterns. However, education in interpretation is needed to improve recognition of purely in-situ disease, since this is an area of increasing importance.

In the multistep progression model, AIS is an intermediate step between AAH and MIA. *KRAS* and *EGFR* mutations hve been demonstrated in up to one-third of AAH, suggesting that these mutations are early events of peripheral adenocarcinomas. These rates of mutation are only slightly different from those seen in AIS, MIA, and invasive adenocarcinomas.[24-26] However, because the definitions of AIS and MIA were established recently, the data on the rates of mutations in these lesions are sparse.

The association between mutations in driver genes such as *EGFR*, *ALK*, and KRAS and the presence of GGO has been studied to some extent. Some studies have demonstrated a significant association between *EGFR* mutation and air bronchogram. In a recent paper, 60% of tumors with GGO harbored the *EGFR* mutation, while only 35% of tumors with GGO were wild-type.[27] In other studies, such correlation was not demonstrated. In a study by Sugano et al, no significant association was found between GGO and *EGFR* mutations ($P = .07$). However, *EGFR* mutations occurred more frequently in male patients with GGO than in men without GGO ($P = .04$).[28] In a study by Ko et al, *EGFR* mutation status was not correlated to GGO proportion of nodules.[29] Pure GGO seems to be a significantly less common finding in patients with *ALK* mutations than it is in those with *EGFR* mutations, and the same is true for patients with *KRAS* mutations.[27,30,31] Ko et al also demonstrated that *ALK* rearrangement is rare in lung cancer with pure GGO nodules.[29] Finally, in a recent study, GGO nodules negative for four driver mutations (*EGFR*, *KRAS*, *ALK*, and *HER2*) were associated with no growth, whereas *EGFR* mutation–positive GGO nodules demonstrated a correlation with growth.[32] Prospective studies are required to further validate the association between GGO nodules and the presence of driver mutations.

Management of GGO Nodules

The increasing use of low-dose chest CT scans and implementation of CT screening for lung cancer have made it increasingly important to have available updated algorithms on the management of such findings as GGO lesions. Several sets of guidelines are already available for the management of subsolid nodules found on CT scans or via CT screening.

In 2013, the Fleischner Society (FS) published their recommendations for the management of subsolid pulmonary nodules detected on CT.[6] These complemented the 2005 FS guidelines on small pulmonary nodules detected on LDCT scans,[33], and together with data from NLST[34] and International Early Lung and Cardiac Action Program (I-ELCAP) protocol guidelines[35] form the basis for the recommendations from the National Comprehensive Cancer Network (NCCN).[36]

Recently, the British Thoracic Society (BTS) also published guidelines for investigation of pulmonary nodules.[37] The

TO PUT THAT INTO CONTEXT

George A. Eapen, MD
MD Anderson Cancer Center
Houston, Texas

GGOs Have Been Around for Years: Why Are They of More Concern Now?

Since the advent of chest computed tomography (CT), physicians have been faced with incidentally discovered ground-glass opacities (GGOs). A plethora of clinical conditions may manifest as transient GGOs that will resolve with the treatment of the underlying disorder. The challenge lies in the management of persistent GGOs, which at the dawn of the lung cancer screening era, are poised to become a major clinical concern. Available evidence suggests that large, growing, or part-solid GGO nodules are likely to harbor malignancy, but the natural history of such malignancies is not clearly delineated, translating to less clinical certainty regarding aggressive sampling and treatment options.

Which Aspects of GGO Management Are Particularly Challenging?

This review crisply collates the available literature and guidelines in the management of persistent GGO nodules, highlighting areas of uncertainty, particularly with reference to follow-up imaging and surgical resection.

A systematic approach, with particular emphasis on patient education and shared decision making, is clearly warranted and can help optimize outcomes. However, the optimal length of follow-up for stable GGO nodules and the optimal curative intent therapy remain uncertain. While surgical resection, specifically lobectomy, is currently the standard of care for early-stage lung cancer, it is not clear that this is necessarily the optimal approach for patients with GGO nodules who are ultimately diagnosed with lung cancer, in whom the tumor biology may be different from that of patients with historically diagnosed lung cancer. The role of more limited surgical resection is being explored, and almost heretically, alternative treatment strategies, such as stereotactic ablative body radiation, are also being considered.

Where Will New Data Provide Greater Clarity?

As we gain more experience, more robustly evidence-based recommendations for follow-up, as well as preferred therapeutic options, can be expected.

guidelines were based on a comprehensive review of the literature and on evidence from case series and reports that each included 50 or more GGO nodules, and from large CT screening trials; predominantly thin-section CT scans were included.

The following is a summary of the guideline recommendations for the management of subsolid nodules, along with the evidence supporting these recommendations.

Scan intervals and length of follow up

With regard to short-term follow-up, the BTS guidelines suggest an initial follow-up CT scan 3 months after detection; the FS guidelines make the same recommendation (however, in both sets of guidelines, this recommendation only applies in GGO nodules of more than 5 mm). The recommendation is based on retrospectively collected data that support 3 months as being an appropriate interval to wait before measuring to determine resolution or growth of a GGO nodule.[38] NCCN recommends yearly follow-up of GGO nodules smaller than 5 mm and initial follow-up in 6 months if nodule size is greater than 5 mm—up through 10 mm.

Pertinent to the issue of long-term follow-up of persistent GGO nodules, studies have showed a significant increase in size (2 mm or more in longest diameter) after the nodules had been stable for more than 2 years.[38] Furthermore, some studies suggest that significant growth can be seen in about one out of four nodules after a median interval of approximately 4 years.[39,40] Thus, the BTS guidelines recommend that GGO nodules be followed for at least 4 years.[37] The FS guidelines recommend annual surveillance CT scans for a minimum of 3 years.[6] The NCCN guidelines recommend annual surveillance for a minimum of 2 years or until the patient is no longer a candidate for definitive treatment (Figure 3).

Size and growth measures predictive of malignancy

Growth in linear measures. Most studies have used linear measurements. An increase of 2 mm or more in the maximum diameter of a GGO nodule was considered significant and suggestive of malignancy. Nodules whose initial size was smaller than 5 mm in maximum diameter were considered benign and required no follow-up.[41]

The NCCN guidelines, however, define nodule growth differently, in a manner dependent on nodule size. For nodules 15 mm or smaller, growth is defined as an increase in the mean diameter of 2 mm or more in any nodule or in the solid portion of a part-solid nodule when compared with the baseline scan. For nodules 15 mm or larger, growth is defined as an increase of 15% in mean diameter when compared with the baseline scan.[36]

Growth in volume. GGO nodules are often slow-growing nodules with higher volume doubling times than are seen in solid nodules. The mean volume doubling time for growing GGO nodules was 769 days in one study and 1,041 days in another.[42,43] Currently, neither the NCCN nor the FS has addressed volumetric analysis or calculations based on volume doubling time.

Growth in mass. A study from the Dutch-Belgian NELSON trial suggests that measurements of the mass of GGO nodules can detect growth earlier than linear and volumetric measures and are subject to less inter-observer variability.[42]. The mass of a nodule can be derived from the CT image by using the nodule Hounsfield Unit value, which is a density measurement; from this value, the mass can be calculated.

The NCCN guidelines recommend annual surveillance for a minimum of 2 years or until the patient is no longer a candidate for definitive treatment

The role of PET-CT

Some studies have shown that the use of F18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT to discriminate between benign and malignant GGO nodules is inappropriate, especially in the case of pure GGO nodules.[43,44] The BTS guidelines suggest that PET/CT may have a role in management if standardized uptake value (SUV) thresholds are lowered. A single study that included 64 pure GGO nodules showed an increase in the accuracy of FDG PET/CT when the SUV threshold was lowered to 0.8.[45] PET has low sensitivity for nodules with a solid component of less than 8 mm.[36]

Nodule risk prediction model

The BTS guidelines were the first to include risk prediction models in the nodule management algorithms. Because of its high area under the curve for small nodules (under 10 mm), use of the Brock model is recommended.[41] The model has been thoroughly validated in a UK population[46] and with data from the Danish Lung Cancer Screening Trial (DLCST).[47] The model is based on data from the low-dose CT screening trial in Canada (Pan-Canadian Early Detection of Lung Cancer Study [PanCan]) and on validation datasets from chemoprevention studies conducted by the British Columbia Cancer Agency (BCCA). A combined 12,029 nodules (144 malignant) were included. In the original PanCan study, predictors for malignancy were nodule size, advanced age, lung cancer in the family, location in the upper lobe, part-solid nodule type, lower nodule count,

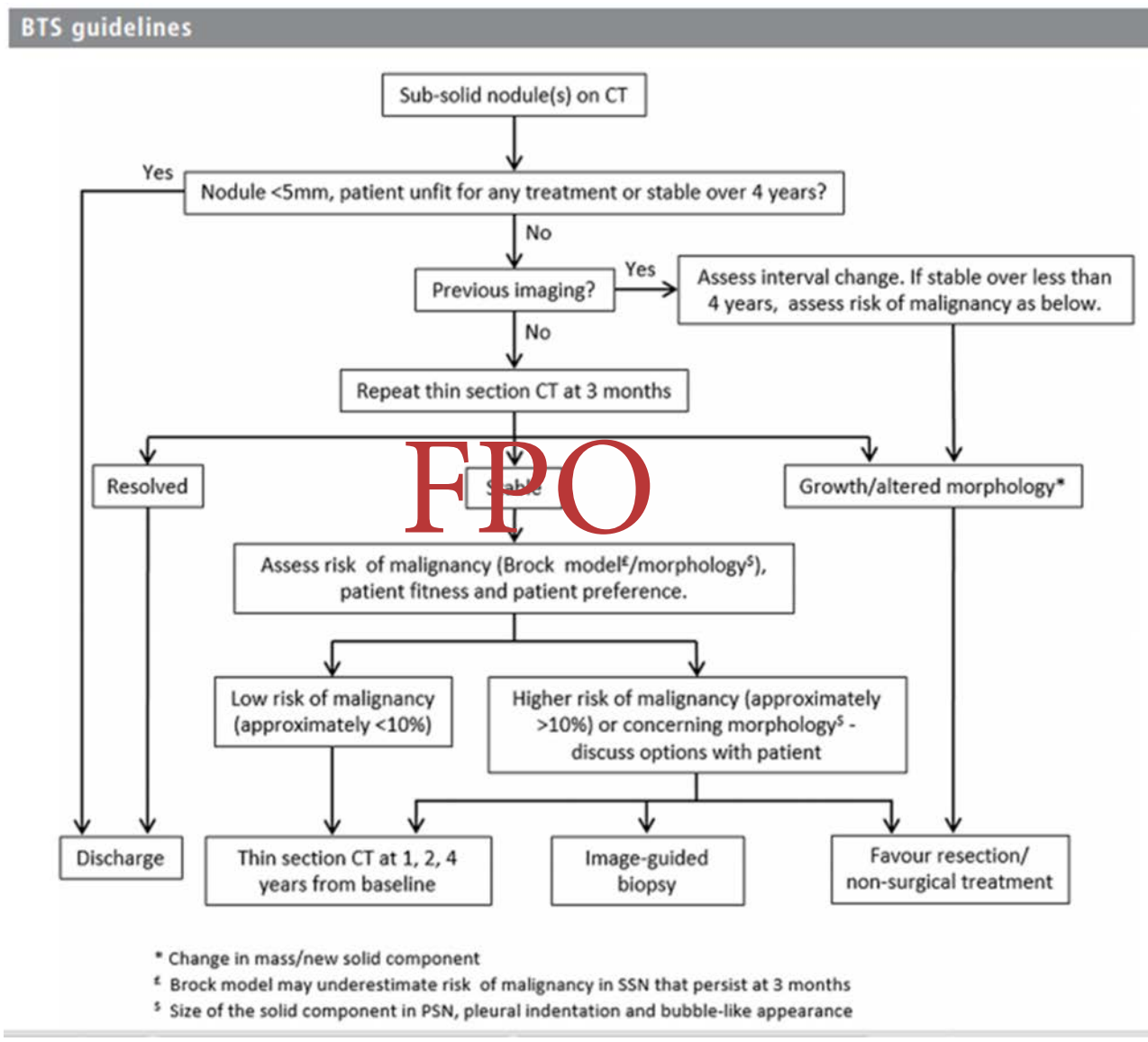

Figure 3. British Thoracic Society Guidelines for the Management of Subsolid Pulmonary Nodules. CT = computed tomography; PSN = part-solid nodule; SSN = subsolid nodule. Reproduced from Baldwin DR, Callister MEJ. The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. Thorax. 2015;70:794-8,[37] with permission from BMJ Publishing Group, Ltd.

and spiculation. Female sex and the presence of visually detected emphysema on CT were also considered malignancy predictors; however, these were not validated in the validation study from DLCST, in which male sex was associated with a greater risk of malignancy and emphysema was not found to be a useful predictor of nodule malignancy. The Brock model is available free of charge at http://www.brocku.ca/lung-cancer-risk-calculator (choose full model).

The BTS guidelines recommend the use of the Brock risk prediction tool if a GGO nodule 5 mm or larger in size is stable after 3 months. If the risk of malignancy is low (less than 10%), imaging follow-up is recommended.[37] However, if the risk is higher

Table. Japan Clinical Oncology Group Strategy for Small Lung Cancers With GGO Characteristics

Tumor Size	C/T Ratio: 0–0.25	C/T Ratio: 0.25–0.5	C/T Ratio: 0.5–1.0
0–2.0 cm	Wide wedge resection (Study ID: JCOG0804)	Segmentectomy (Study ID: JCOG1211)	Lobectomy vs segmentectomy (Study ID: JCOG0802)
2.0–3.0 cm	Segmentectomy (Study ID: JCOG1211)	Segmentectomy (Study ID: JCOG1211)	Standard lobectomy
> 3.0 cm	Standard lobectomy	Standard lobectomy	Standard lobectomy

C/T = consolidation/tumor; GGO = ground-glass opacity.
Data from: Asamura H. Presentation at 16th World Conference on Lung Cancer.[70]

(greater than 10%), consideration of a more invasive diagnostic approach is recommended.

Results from the Dutch-Belgian NELSON trial

In 2014, researchers from the Dutch-Belgian NELSON trial analyzed the way in which they had used low-dose CT in evaluating and handling the GGO nodules in the study population of this large lung cancer screening trial.[48] Included in the analysis were 7,135 participants from the screening group. During the trial, 264 GGO nodules were registered, of which 117 persisted after 3 months of follow-up. Of these, 69 were pure GGO nodules and 48 were part-solid GGO nodules. Twenty of the pure GGO nodules developed into part-solid GGO nodules. A total of 33 GGO nodules were resected (11 pure GGO nodules and 22 part-solid GGO nodules); 28 (85%) were AIS or invasive carcinoma. Eighty-four of the nonresected GGO nodules (51 pure GGO nodules and 33 part-solid GGO nodules) were followed in accordance with the study protocol algorithm.[49] None of the unresected GGO nodules developed into symptomatic lung cancer; however, six participants died of pulmonary adenocarcinoma diagnosed in a solid nodule elsewhere in the lung parenchyma. The median follow-up period in the patients with unresected GGO nodules was 95 months. The research group found that their strategy—which involved close follow-up and a cut-off level for further investigation of 30% increase in volume of the solid component—could be considered safe.

Natural history of GGO nodules

Growth and solid transformation of GGO nodules are indicators of malignancy; however, most GGO nodules remain unchanged, and this is one of the reasons why the management GGO nodules can be challenging. A study consisting of 122 screen-detected GGO nodules showed that 90% of nodules did not grow during long-term follow-up (median follow-up, 59 months).[50] Most GGO nodules thus have an indolent clinical course[51]; this is especially true in screening settings, where the participants are without symptoms. Selective surgery and longer (over 4 years) follow-up of GGO nodules is thus crucial to insure optimal, safe management.[40,52]

Localization, Marking, and Surgical Management of GGO Nodules

Suspicious GGO nodules may have to be surgically removed via video-assisted thoracoscopic surgery (VATS) for diagnostic or therapeutic reasons. However, GGO nodules are often difficult to locate due to their size and morphology. The preferred surgical procedure is VATS in combination with a marking of the GGO nodule. Most of the evidence regarding markers is derived from studies of peripherally located solid nodules smaller than 15 mm. It is generally assumed that the techniques used in the latter setting will also be effective in cases of GGO nodules.[53] The marking consists of CT-guided injection of 0.2 mL of methylene blue at the periphery of the nodule in combination with a small amount of dye at the subpleural region at the level of the nodule to serve as guidance for the surgeon.[54] In a recent prospective randomized trial, CT-guided percutaneous placement of microcoil markers in combination with fluoroscopic-guided VATS resection was significantly better than procedures in which nodule localization was via finger palpation only in small (mean nodule diameter, 12 mm) solid and subsolid nodules (93% vs 48%; $P < .01$).[53] Other techniques available are intraoperative ultrasonography,[55] hook wire placement,[56] injection of lipidol,[57] and injection of radioisotope.[58] Centrally located GGO lesions are more difficult to resect and may in rare cases require a diagnostic lobectomy, even though this should be the diagnostic approach of last resort.[59]

The current guidelines recommend lobectomy with systematic lymph node dissection as the minimal resection in cases of stage I/II invasive carcinoma.[60] In recent years, improvements in CT scanning resolution, combined with increased use of CT screening, has led to the increased detection of GGO lesions that represent noninvasive or MIA types of lung cancer with a favorable prognosis.[8,61] In a CT screening context, the indication for surgery should always be carefully considered, and the decision should be made by a multidisciplinary board.[62] This is a necessary precaution in order to avoid resection of nonmalignant lesions, which if left alone might have regressed/disappeared and could in principle represent instances of the overdiagnosis of lung cancer. However, when a malignant diagnosis has been made, surgery is the primary curative treatment option. In some cases, sublobar resection may offer the same long-term survival as lobectomy, and without an increase in the likelihood of local recurrence.[63,64] In the past, sublobar resection has primarily been reserved for operable but high-risk patients in whom the optimal surgical approach must be modified. However in recent years, especially in Japan, considerable research has gone into the

evaluation of sublobar resections in non–high-risk patients.[65] The potential benefits of sublobar resection would be to spare healthy lung tissue, making for better respiratory capacity, and to allow for the possibility of future surgical treatment in the event of a new primary lung cancer.

It is possible to use radiologic criteria to identify an early noninvasive adenocarcinoma—eg, when the GGO nodule size is less than 2 cm and the C/T ratio is below 0.25 (cT1a), or when the C/T ratio is below 0.5 in a GGO nodule less than 3 cm in size (cTa-b).[8] In these patients, wide wedge resection is being compared with segmentectomy in an ongoing prospective, randomized trial conducted by the Japan Clinical Oncology Group (Table).[65] For radiologically invasive lung tumors (cTaN0M0) 2 cm or less in diameter and a C/T ratio greater than 0.5, lobectomy vs segmentectomy is being investigated in another randomized trial conducted by the Japan Clinical Oncology Group (Table).[66] In the United States, the Cancer and Leukemia Group B 140503 trial (ClinicalTrials.gov identifier: NCT00499330) is comparing lobectomy vs wedge resection or segmentectomy. With more extensive use of CT screening, it is expected that more GGO lesions will be detected, and hence the indications for sublobar resection will need to be considered more often. However, it is important that the oncologic benefit of the surgical procedure be monitored by conducting adequate follow-up and registering results, to make possible the systematic evaluation of the procedures used. Segmentectomy is oncologically superior to a wedge resection, since it provides wider resection margins and a lower local recurrence rate.[67] If a wedge resection is performed, it should be done with a resection margin greater than 2 cm, or greater than the maximal tumor diameter.[68,69]

Conclusions

GGO nodules remain a diagnostic challenge, and therefore a more systematic approach is necessary to ensure an optimal work-up. Persisting GGO nodules larger than 5 mm should be followed for at least 4 years. PET/CT has limited value in the diagnostic work-up of GGO nodules. Growth of more than 2 mm in maximal diameter is considered significant. Development of a solid component in a pure GGO nodule, or growth of a preexisting solid component in a part-solid GGO nodule, is predictive of invasive malignancy. In such cases, invasive techniques such as CT-guided biopsy or nodule removal by VATS should be considered. The current standard of care for surgical treatment of early lung cancer (cT1a-bN0M0) is still VATS lobectomy. Recent research has shown that some GGO lesions with low C/T ratios may be treated by sublobar resection. However, final recommendations with regard to this must await the results of ongoing randomized trials in the United States and Japan.

Financial Disclosure: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

REFERENCES

1. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409.
2. Fintelmann FJ, Bernheim A, Digumarthy SR, et al. The 10 pillars of lung cancer screening: rationale and logistics of a lung cancer screening program. Radiographics. 2015;35:1893-908.
3. Zhao SJ, Wu N. Early detection of lung cancer: low-dose computed tomography screening in China. Thorac Cancer. 2015;6:385-9.
4. Infante M, Lutman RF, Imparato S, et al. Differential diagnosis and management of focal ground-glass opacities. Eur Respir J. 2009;33:821-7.
5. Verschakelen JA, De Wever W. Computed tomography of the lung: a pattern approach. In: Baert AL, Knauth M, Sartor K, editors. Medical radiology, diagnostic imaging. Heidelberg, Germany: Springer; 2007.
6. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology. 2013;266:304-17.
7. Lee HY, Choi YL, Lee KS, et al. Pure ground-glass opacity neoplastic lung nodules: histopathology, imaging, and management. AJR Am J Roentgenol. 2014;202:W224-W233.
8. Asamura H, Hishida T, Suzuki K, et al. Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of the Japan Clinical Oncology Group 0201. J Thorac Cardiovasc Surgery. 2013;146;24-30.
9. Ridge CA, Alexander A, Eisenberg B. Mosaic attenuation. AJR Am J Roentgenol. 2011;197:W970-W977.
10. Travis WD, Brambilla E, Burke AP, et al, editors. WHO classification of tumours of the lung, pleura, thymus and heart. 4th ed. Geneva: WHO Press;2015.
11. Kadota K, Villena-Vargas J, Yoshizawa A, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. Am J Surg Pathol. 201r;38:448-60.
12. Tsutani Y, Miyata Y, Nakayama H, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. J Thorac Cardiovasc Surg. 2012;143:607-12.
13. Lim HJ, Ahn S, Lee KS, et al. Persistent pure ground-glass opacity lung nodules >/= 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. Chest. 2013;144:1291-9.
14. Lee HY, Choi YL, Lee KS, et al. Pure ground-glass opacity neoplastic lung nodules: histopathology, imaging, and management. AJR Am J Roentgenol. 2014;202:W224-W233.
15. Isaka T, Yokose T, Ito H, et al. Comparison between CT tumor size and pathological tumor size in frozen section examinations of lung adenocarcinoma. Lung Cancer. 2014;85:40-6.
16. Lim HJ, Ahn S, Lee KS, et al. Persistent pure ground-glass opacity lung nodules >/= 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. Chest. 2013;144:1291-9.
17. Lee HY, Choi YL, Lee KS, et al. Pure ground-glass opacity neoplastic lung nodules: histopathology, imaging, and management. AJR Am J Roentgenol. 2014;202:W224-W233.
18. Isaka T, Yokose T, Ito H, et al. Comparison between CT tumor size and pathological tumor size in frozen section examinations of lung adenocarcinoma. Lung Cancer. 2014;85:40-6.
19. Warth A, Muley T, Meister M, et al. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. J Clin Oncol. 2012;30:1438-46.
20. Yoshizawa A, Sumiyoshi S, Sonobe M, et al. Validation of the IASLC/ATS/ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: analysis of 440 Japanese patients. J Thorac Oncol. 2013;8:52-61.
21. Tsao MS, Marguet S, Le TG, et al. Subtype classification of lung adenocarcinoma predicts benefit from adjuvant chemotherapy in patients undergoing complete resection. J Clin Oncol. 2015;33:3439-46.
22. Thunnissen E, Beasley MB, Borczuk AC, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. Mod Pathol. 2012;25:1574-83.
23. Duhig EE, Dettrick A, Godbolt DB, et al. Mitosis trumps T stage and proposed International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification for prognostic value in resected stage 1 lung adenocarcinoma. J Thorac Oncol. 2015;10:673-81.
24. Yoshida Y, Shibata T, Kokubu A, et al. Mutations of the epidermal growth factor receptor gene in atypical adenomatous hyperplasia and bronchioloalveolar carcinoma of the lung. Lung Cancer. 2005;50:1-8.
25. Soh J, Toyooka S, Ichihara S, et al. Sequential molecular changes during multistage pathogenesis of small peripheral adenocarcinomas of the lung. J Thorac Oncol. 2008;3:340-7.

26. Sakamoto H, Shimizu J, Horio Y, et al. Disproportionate representation of KRAS gene mutation in atypical adenomatous hyperplasia, but even distribution of EGFR gene mutation from preinvasive to invasive adenocarcinomas. J Pathol. 2007;212:287-94.
27. Rizzo S, Petrella F, Buscarino V, et al. CT Radiogenomic characterization of EGFR, K-RAS, and ALK mutations in non-small cell lung cancer. Eur Radiol. 2016;26:32-42.
28. Sugano M, Shimizu K, Nakano T, et al. Correlation between computed tomography findings and epidermal growth factor receptor and KRAS gene mutations in patients with pulmonary adenocarcinoma. Oncol Rep. 2011;26:1205-11.
29. Ko SJ, Lee YJ, Park JS, et al. Epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangements in lung cancer with nodular ground-glass opacity. BMC Cancer. 2014;14:312.
30. Zhou JY, Zheng J, Yu ZF, et al. Comparative analysis of clinicoradiologic characteristics of lung adenocarcinomas with ALK rearrangements or EGFR mutations. Eur RadioI. 2015;25:1257-66.
31. Glynn C, Zakowski MF, Ginsberg MS. Are there imaging characteristics associated with epidermal growth factor receptor and KRAS mutations in patients with adenocarcinoma of the lung with bronchioloalveolar features? J Thorac Oncol. 2010;5:344-8.
32. Kobayashi Y, Mitsudomi T, Sakao Y, Yatabe Y. Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules: the differences between nodules with and without growth. Ann Oncol. 2015;26:156-61.
33. MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005;237:395-400.
34. Aberle DR, Berg CD, Black WC, et al; National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. Radiology. 2011; 258:243-53.
35. Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med. 2006;355:1763-71.
36. Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thorac Surg Clin. 2015;25:185-97. http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf. Accessed February 11, 2016.
37. Baldwin DR, Callister MEJ. The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. Thorax. 2015;70:794-8.
38. Hiramatsu M, Inagaki T, Inagaki T, et al. Pulmonary ground-glass opacity (GGO) lesions—large size and a history of lung cancer are risk factors for growth. J Thorac Oncol. 2008;3:1245-50.
39. Kobayashi Y, Sakao Y, Deshpande GA, et al. The association between baseline clinical-radiological characteristics and growth of pulmonary nodules with ground-glass opacity. Lung Cancer. 2014;83:61-6.
40. Lee SW, Leem C-S, Kim TJ, et al. The long-term course of ground-glass opacities detected on thin-section computed tomography. Respir Med. 2013;107:904-10.
41. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369:910-9.
42. de Hoop B, Gietema H, van de Vorst S, et al. Pulmonary ground-glass nodules: increase in mass as an early indicator of growth. Radiology. 2010;255:199-206.
43. Veronesi G, Travaini LL, Maisonneuve P, et al. Positron emission tomography in the diagnostic work-up of screening-detected lung nodules. Eur Respir J. 2015;45:501-10.
44. Nomori H, Watanabe K, Ohtsuka T, et al. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung Cancer. 2004;45:19-27.
45. Ichinose J, Kohno T, Fujimori S, et al. Invasiveness and malignant potential of pulmonary lesions presenting as pure ground-glass opacities. Ann Thorac Cardiovasc Surg. 2014;20:347-52.
46. Al-Ameri A, Malhotra P, Thygesen H, et al. Risk of malignancy in pulmonary nodules: a validation study of four prediction models. Lung Cancer. 2015;89:27-30.
47. Winkler Wille MM, van Riel SJ, Saghir Z, et al. Predictive accuracy of the PanCan lung cancer risk prediction model—external validation based on CT from the Danish Lung Cancer Screening Trial. Eur Radiol. 2015;25:3093-9.
48. Scholten ET, de Jong PA, de Hoop B, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? Eur Respir J. 2015;45:765-73.
49. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med. 2009;361:2221-9.
50. Chang B1, Hwang JH, Choi YH, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. Chest. 2013;143:172-8
51. Gulati CM, Schreiner AM, Libby DM, et al. Outcomes of unresected ground-glass nodules with cytology suspicious for adenocarcinoma. J Thorac Oncol. 2014;9:685-91.
52. Lee SW, Leem C-S, Kim TJ, et al. The long-term course of ground-glass opacities detected on thin-section computed tomography. Respir Med. 2013;107:904-10.
53. Finley RJ, Mayo JR, Grant K, et al. Preoperative computed tomography-guided microcoil localization of small peripheral pulmonary nodules: a prospective randomized controlled trial. J Thorac Cardiovasc Surg. 2015;149;26-32.
54. McConnell PI, Feola GP, Meyers RI. Methylene blue-stained autologous blood for needle localization and thoracoscopic resection of deep pulmonary nodules. J Pediatr Surg. 2002;37;1729-31.
55. Khereba M, Ferraro P, Duranceau A, et al. Thoracoscopic localisation of intra-parenchymal pulmonary nodules using direct intracavitary thoracoscopic ultrasomography prevents conversion of VATS procedures to thoracotomy in selected patients. J Thorac Cardiovasc Surg. 2012;144;1160-5.
56. Mioyoshi K, Toyooka S, Gobara H, et al. Clinical outcomes of a short hook wire and suture marking system in thoracoscopic resection for pulmonary nodules. Eur J Cardiothorac Surg. 2009;36;378-82.
57. Watanabe K, Nomori H, Ohtsuka T, et al. Usefulness and complications of computed tomography–guided lipiodol making for fluoroscopy-assisted thoracoscopic resection of small pulmonary nodules: experience with 174 nodules. J Thorac Cardiovasc Surg. 2006;132;320-4.
58. Gonfiotti A, Davini E, Vaggelli L, et al. Thoracoscopic localization techniques for patients with solitary pulmonary nodules: hookwire versus radio-guided surgery. Eur J Cardthorac Surg. 2007;32;843-7.
59. Petersen RH, Hansen HJ, Dirksen A, Pedersen JH. Lung cancer screening and video-assisted thoracic surgery. J Thorac Oncol. 2012;7;1026-31.
60. Lim E, Baldwin D, Beckles, Duffy J, et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010;65(suppl III):iii1-iii27.
61. Suzuki K, Kusumoto M, Watanabe S, et al. Radiological classification of small adenocarcinoma of the lung. Radiologic-pathologic correlation and its prognostic impact. Ann Thorac Surg. 2006;81;413-9.
62. Field JK, Smith RA, Aberle DR, et al. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report. J Thorac Oncol. 2012;7:10-9.
63. Tsutani Y, Miyata Y, Nakayama H, et al. Oncological outcomes of segmentectomy compared with lobectomy for clinical stage IA lung adenocarcinoma: propensity score-matched analysis in a multicenter study. J Thorac Cardiovasc Surg. 2013;146;358-64.
64. Tsutani Y, Miyata Y, Nakayama H, et al. Appropriate sublobar resection choice ground glass opacity–dominant clinical stage IA adenocarcinoma. Wedge resection or segmentectomy. Chest. 2014;145:66-71.
65. Sakurai H, Asamura H. Sublobar resection for early-stage lung cancer. Transl Lung Cancer Res. 2014;3;164-72.
66. Nakamura K, Sajii H, Nakajima R, et al. A phase III randomised trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607). Jpn J Clin Oncol. 2010;40;271-4.
67. Kent M, Landrenau R, Mandrekar, et al. Segmentectomy versus wedge resection for non-small cell lung cancer in high-risk operable patients. Ann Thorac Surg. 2013;96;1747-55.
68. Sawabata N, Ohta M, Matsumura A, et al Optimal distance of malignant negative margin in excision of non-small cell lung cancer: a multicenter prospective study. Ann Thorac Surg. 2004;77;415-20.
69. Schuchert MJ, Pettiford BL, Keeley S, et al Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer. Ann Thorac Surg. 2007;84;926-32; discussion 932-3.
70. Asamura H. Rationale for performing sublobar resection for early lung cancer. Presentation at 16th World Conference on Lung Cancer; 2015 Sep 6–9; Denver, CO.

More Opaque than Clear: Reality is Always Cloaked in Shades of Gray

Frank C. Detterbeck, MD[1,2]

The review by Pedersen and colleagues on ground-glass opacity (GGO) lung nodules[1] is timely, addressing a clinical scenario that clinicians are increasingly confronted with: how to appropriately manage the patient with an incidentally detected GGO nodule. I commend the authors for assembling a broad yet concise review of data that can help guide decision making in this setting. However, I think that in reality, many of the concepts presented are not as clear-cut as depicted; we must be thoughtful and nuanced in our judgment when managing these patients.

This commentary reflects on the review article on page 266.

The correlation between radiographic appearance and histologic diagnosis is far from reliable. Among resected pure GGO nodules, adenocarcinoma in situ (AIS) was diagnosed in 20% to 59%, minimally invasive adenocarcinoma (MIA) in 20% to 32%, and invasive adenocarcinoma in 39% to 48%.[2-4] Earlier studies of resected pure GGO nodules found that 10% to 30% were benign, 5% to 70% were atypical adenomatous hyperplasia, 20% to 70% were bronchioloalveolar carcinoma, and 10% to 30% were invasive adenocarcinoma.[5] There is moderate interobserver variability in the histologic classification: in a study evaluating the presence of invasion in 64 cases as assessed by 28 thoracic pathologists, complete agreement was seen in 10%, and less than 10% discordance in 29% (with use of a three-point scale: "probable and definite invasion," "unclear," "probably or definitely not invaded").[6] Furthermore, radiographic appearance is significantly affected by many factors, such as CT section thickness, window wettings, and radiation dose.[7] Thus, equating a pure GGO nodule with AIS and a part-solid GGO nodule that has a solid component of less than 5 mm with MIA is a gross oversimplification.

The underlying assumption in the review by Pedersen et al is that the diagnosis is black and white: benign or invasive lung cancer. Yet lung cancer exhibits a wide spectrum of behavior, from inconsequential to nonaggressive, typically aggressive, and very aggressive lung cancer. The proportion of "well-behaved" cancers has clearly been increased by the advent of CT screening.[8] The decision to treat must consider both the aggressiveness of the lung cancer and competing risks (comorbidities). Furthermore, the spectrum of nonaggressiveness/aggressiveness may confound the extent-of-resection data: for example, is survival after wedge resection for a pure GGO nodule good simply because the tumor was inconsequential anyhow? We have to learn to think of lung cancer in shades of gray rather than simply as malignant vs benign, or invasive vs noninvasive.

We have to learn to think of lung cancer in shades of gray rather than simply as malignant vs benign, or invasive vs noninvasive

The view that it is only a matter of time until a GGO nodule progresses may not be correct. Kobayashi et al studied 108 GGO nodules that were followed for up to 10 years: only about one-third demonstrated progression (which manifested within 3 years in all cases).[9] Other research suggests that there may be two different populations of GGO nodules, with different mutational patterns; only about one-third are of the type that appears likely to progress.[10,11]

Observing a potentially nonaggressive lung cancer for a period of time is an appealing approach, since this allows the degree of change to guide management. However, small changes can be hard to assess. The appearance of a GGO nodule varies with the degree of inspiration and scanner parameters, and assessment is hampered by inter/intra-observer variability. Even for solid tumors, data show that false-positive and false-negative assessments of growth are on the order of 10% to 50%,[12] and that inter- and intra-observer consistency are poor for size differences of less than 1.5 mm up to 2 mm.[13,14] GGO nodules are even more difficult to measure reproducibly, and volumetric programs generally do not work well (with interscan variability of ~35% and intra/inter-observer variability of 20% to 40%).[15,16] Furthermore, growth must be evaluated in light of the time inter-

[1]Yale Medical School, New Haven, Connecticut
[2]Yale Cancer Center, New Haven, Connecticut

val involved: does a GGO nodule that has grown 1 to 2 mm over 5 years constitute a life-threatening lung cancer?

A growing body of data shows that prognosis correlates primarily with the solid component of a GGO nodule and with the invasive component of adenocarcinoma.[7,17-20] In fact, in the new (8th edition) American Joint Committee on Cancer staging system (due out in mid-2016), T will be determined by the solid (as determined by imaging)/invasive (as determined by pathology) component.[7] Thus, the development and the size of a solid component appear to be much more important than the GGO/lepidic component, calling into question the clinical importance of growth (typically slow) of a pure GGO nodule.

Data from CT screening show a marked increase in the proportion of patients with a long volume doubling time (VDT) compared with VDTs in patients with regularly detected lung cancers.[8] Among pure GGO lesions, 50% to 90% are tumors with a VDT of more than 400 days, and VDT is greater than 800 days in 20% to 50%.[8] Limited data are available regarding lung cancers incidentally detected on CT not associated with a screening program, but these data suggest a stage distribution and survival similar to the values seen in CT screening programs.[21,22]

In summary, I offer several thoughts regarding the management of GGO nodules:

1. Focus on the solid component. This appears to correlate better with the more typical behavior of lung cancer, and the new stage classification will focus on the solid-appearing or invasive component of a cancer.

2. Be sure of what you see. There is a lot of variability in the assessment of small imaging changes. It is generally best to evaluate several scans over a period of time to be sure that a perceived change is real.

3. Is it a cancer that matters? The spectrum of lung cancer, especially of cancer that presents as a GGO nodule, includes very indolent cancers. The rate of growth must be balanced against comorbidities and competing risks when making management decisions.

Financial Disclosure: The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

REFERENCES

1. Pedersen JH, Saghir Z, Winkler Wille MM, et al. Ground-glass opacity lung nodules in the era of lung cancer CT screening. Oncology (Williston Park). 2016;30:266-74.
2. Son JY, Lee HY, Lee KS, et al. Quantitative CT analysis of pulmonary ground-glass opacity nodules for the distinction of invasive adenocarcinoma from pre-invasive or minimally invasive adenocarcinoma. PLoS One. 2014;9:e104066.
3. Lim H-j, Ahn S, Lee KS, et al. Persistent pure ground-glass opacity lung nodules ≥ 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. Chest. 2013;144:1291-99.
4. Mimae T, Miyata Y, Tsutani Y, et al. What are the radiologic findings predictive of indolent lung adenocarcinoma? Jpn J of Clin Oncol. 2015;45:367-72.
5. Detterbeck FC, Homer RJ. Approach to the ground-glass nodule. Clin Chest Med. 2011;32:799-810.
6. Thunnissen F, Beasley M, Borczuk AC, et al. Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. Mod Pathol. 2012;25:1574-83.
7. Travis D, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for coding T categories for adenocarcinoma in situ and minimally invasive adenocarcinoma, and for measurement of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2016. [In press]
8. Detterbeck F, Gibson C. Turning gray: the natural history of lung cancer over time. J Thorac Oncol. 2008;3:781-92.
9. Kobayashi Y, Fukui T, Ito S, et al. How long should small lung lesions of ground-glass opacity be followed? J Thorac Oncol. 2013;8:309-14.
10. Yatabe Y, Borczuk AC, Powell CA. Do all lung adenocarcinomas follow a stepwise progression? Lung Cancer. 2011;74:7-11.
11. Kobayashi Y, Mitsudomi T, Sakao Y, Yatabe Y. Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules: the differences between nodules with and without growth. Ann Oncol. 2015;26:156-61.
12. Jennings SG, Winer-Muram HT, Tarver RD, Farber MO. Lung tumor growth: assessment with CT—comparison of diameter and cross-sectional area with volume measurements. Radiology. 2004;231:866-71.
13. Nietert PJ, Ravenel JG, Leue WM, et al. Imprecision in automated volume measurements of pulmonary nodules and its effect on the level of uncertainty in volume doubling time estimation. Chest. 2009;135:1580-87.
14. Revel M-P, Bissery A, Bienvenu M, et al. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology. 2004;231:453-58.
15. Oda S, Awai K, Murao K, et al. Computer-aided volumetry of pulmonary nodules exhibiting ground-glass opacity at MDCT. AJR Am J Roentgenol. 2010;194:398-406.
16. Kim H, Park CM, Woo S, et al. Pure and part-solid pulmonary ground-glass nodules: measurement variability of volume and mass in nodules with a solid portion less than or equal to 5 mm. Radiology. 2013;269:585-93.
17. Murakawa T, Konoeda C, Ito T, et al. The ground glass opacity component can be eliminated from the T-factor assessment of lung adenocarcinoma. Eur J Cardiothorac Surg. 2013;43:925-32.
18. Tsutani Y, Miyata Y, Mimae T, et al. The prognostic role of pathologic invasive component size, excluding lepidic growth, in stage I lung adenocarcinoma. J Thorac Cardiovasc Surg. 2013;146:580-85.
19. Tsutani Y, Miyata Y, Nakayama H, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. J Thorac Cardiovasc Surg. 2012;143:607-12.
20. Maeyashiki T, Suzuki K, Hattori A, et al. The size of consolidation on thin-section computed tomography is a better predictor of survival than the maximum tumour dimension in resectable lung cancer. Eur J Cardiothorac Surg. 2013;43:915-18.
21. Raz DJ, Glidden DV, Odisho A, Jablons DM. Clinical characteristics and survival of patients with surgically resected, incidentally detected lung cancer. J Thorac Oncol. 2007;2:125-30.
22. Kawachi RMD, Watanabe S-iMD, Asamura HMD. Clinicopathological characteristics of screen-detected lung cancers. J Thorac Oncol. 2009;4:615-19.

RELATED FEATURES:
T.K.: http://bit.ly/
T.K.: http://bit.ly/