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ABSTRACT

Objective: Lung cancers that present as radiographic subsolid nodules represent a subtype with distinct biological behavior and outcomes. The objective of this document is to review the existing literature and report consensus among a group of multidisciplinary experts, providing specific recommendations for the clinical management of subsolid nodules.

Methods: The American Association for Thoracic Surgery Clinical Practice Standards Committee assembled an international, multidisciplinary expert panel composed of radiologists, pulmonologists, and thoracic surgeons with established expertise in the management of subsolid nodules. A focused literature review was performed with the assistance of a medical librarian. Expert consensus statements were developed with class of recommendation and level of evidence for each of 4 main topics: (1) definitions of subsolid nodules (radiology and pathology), (2) surveillance and diagnosis, (3) surgical interventions, and (4) management of multiple subsolid nodules. Using a modified Delphi method, the statements were evaluated and refined by the entire panel.

Results: Consensus was reached on 17 recommendations. These consensus statements reflect updated insights on subsolid nodule management based on the latest literature and current clinical experience, focusing on the correlation between radiologic findings and pathological classifications, individualized subsolid nodule surveillance and surgical strategies, and multimodality therapies for multiple subsolid lung nodules.

Conclusions: Despite the complex nature of the decision-making process in the management of subsolid nodules, consensus on several key recommendations was achieved by this American Association for Thoracic Surgery expert panel. These recommendations, based on evidence and a modified Delphi method, provide guidance for thoracic surgeons and other medical professionals who care for patients with subsolid nodules. (J Thorac Cardiovasc Surg 2024; -:1-17)

The complexity of managing lung cancers presenting as subsolid lung nodules.

CENTRAL MESSAGE

The diagnosis, staging, surgical management, and surveillance of lung cancers presenting as radiographic subsolid nodules must be tailored to the unique biology of the disease.

PERSPECTIVE

Lung cancers that present as radiographic subsolid nodules represent a subtype with distinct biological behavior and outcomes. The management of subsolid nodules is critically important considering the increasing incidence and the lack of clinical consensus regarding this topic.

See Commentary on page XXX.

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The ever-expanding application of computed tomography (CT) imaging of the chest, both in indication and frequency, has increased the identification of incidental lung nodules, including indeterminate subsolid nodules.\(^1,2\) As a nonspecific radiologic finding, subsolid nodules can either represent benign disease or malignancy. Lung adenocarcinoma manifesting as subsolid lesions is generally considered to be more indolent and correlated with better long-term survival.\(^3\) Therefore, the primary course for most screen-detected subsolid nodules is CT surveillance. However, details of surveillance strategies—including the optimal interval between scans, the total duration of surveillance, as well as the potential role of pre-resection biopsy for diagnosis—remain controversial.\(^4,5\) In addition, concerns have been raised regarding the limitations of relying on only 2 main factors for determining the management of subsolid nodules in most guidelines: size and the presence of a solid component. Moreover, the precise role of surgery in the management of subsolid nodules is relatively less well-defined. Another major concern is the overdiagnosis of nonsolid (ie, pure ground-glass) lung adenocarcinomas; because of their slow-growing course, overdiagnosis may also lead to overtreatment.\(^6\)

Despite recent developments and ongoing debate concerning pertinent clinical questions, there is still a lack of consensus regarding the optimal management strategies for patients with subsolid nodules. This American Association for Thoracic Surgery (AATS) expert consensus document provides recommendations for surveillance and surgical intervention for subsolid nodules while also identifying opportunities for future research.

**METHODS**

**Assembly of an International Expert Writing Group**

The AATS Clinical Practice Standards Committee brought together an international, multidisciplinary writing group composed of radiologists, pulmonologists, and thoracic surgeons with expertise in the identification and treatment of subsolid nodules, and appointed 2 co-chairs (H.C. and J.Y.). All members of this expert panel completed conflict of interest disclosures (Appendix E1).

**Formulation of Clinical Topics and PICO (Population, Intervention, Comparison, and Outcome) Questions**

After selecting the writing group, the co-chairs generated an outline resulting in 4 topics addressing the spectrum of management of subsolid nodules: (1) the definition of subsolid nodules—radiology and pathology, (2) surveillance and diagnosis, (3) surgical intervention, and (4) managing multiple subsolid nodules. Panel members were divided into corresponding subgroups covering each topic. With the assistance of a medical librarian, we conducted PubMed searches that combined key words and Medical Subject Headings for ground-glass opacity (GGO), ground-glass nodule, ground-glass, part-solid, subsolid, and nonsolid; lung; lung, radiology, and pathology; surgery, surveillance; wedge resection, segmentectomy, and lobectomy; postsurgical period; and radiation, ablation, and stereotactic body radiation therapy (SBRT). The searches were restricted to human studies in English and published since 1990. The searches produced 619 results, and other individual papers were also added to the body of literature by the group members as appropriate. In total, 167 papers met the inclusion criteria for the project. Each subgroup created recommendations using the patient intervention comparison outcome (PICO) format, assigned classification of...
recommendation (COR), and determined the level of evidence (LOE) according to guidance from AATS and Grading of Recommendations Assessment, Development and Evaluation approaches\(^7\),\(^8\) (Figure 1).\(^10\) Each statement was critically examined and revised by the entire group.

### Development of an Expert Consensus Document

The expert consensus panel was then asked to evaluate each statement on a 5-point Likert scale (graded as 1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree). According to the modified Delphi method process,\(^11\) at least 80\% participation was required to achieve a 75\% consensus rate (“agree” or “strongly agree”). A second or third round of voting after proper revision was used if the threshold was not achieved.\(^9\) Once the consensus statements and their COR and LOE were determined, each expert member from the subgroups contributed substantially to the writing of sections. The document was finalized by the co-chairs. Before the document was finally approved by the AATS Clinical Practice Standards Committee, the writing group and

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RESULTS

Section 1: Definition of Subsolid Lung Nodules—Radiology and Pathology

This section establishes radiology and pathology terminology used throughout the document; therefore, no COE or LOE are assigned to these statements (Table 1).5,12-19,27,35

**Statement 1.** A subsolid lung nodule is defined as a CT-identified focal GGO with variable solid components within which the presence of underlying pulmonary vessels or bronchial structures remain visible.

**Statement 2.** Subsolid lung nodules are divided into 2 categories: nonsolid (ie, pure GGO without any solid component) and part-solid nodule (PSN) with both solid and nonsolid components.

The most widely accepted definitions of pulmonary subsolid nodules were proposed by the Fleischner society in 2008.12 The current consensus classification divides subsolid nodules into 2 main categories: PSNs, characterized by nodules with both GGO and solid components, and nonsolid nodules (also known as pure GGO), corresponding to nodules without any solid component.5,13-15 Recent studies have introduced the concept of a heterogeneous ground-glass nodule (hGGN) as a nodular entity that displays a GGO component and a solid portion exclusively in the lung window.16,17 In addition, the term “real part-solid nodule” (rPSN) has been used to describe GGO nodules with a solid component present in both the lung and mediastinal windows.18

**Statement 3.** For subsolid nodules pathologically diagnosed as malignant diseases, nonsolid (ie, ground-glass) components tend to correspond to atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS) versus solid components, which tend to correspond with invasive patterns. Minimally invasive adenocarcinoma (MIA), defined as a lepidic tumor with <5 mm of stromal invasion, may be associated with a radiologically visualized solid component, but not always. For subsolid nodules, increasing CT attenuation, increasing solid component, or a solid portion measurable in the mediastinal window raise the suspicion of invasive adenocarcinoma.

**Statement 4.** For nonsolid nodules (ie, pure GGOs), nodule growth is defined as an absolute increase in mean diameter >1.5 mm (average of longest and shortest diameters) or the appearance of a solid component. For PSNs, the nodule growth is defined as an absolute increase in mean nodule or solid component diameter >1.5 mm.

For subsolid nodules pathologically diagnosed as malignant diseases, a pure GGO component is likely to represent a preinvasive lesion such as AAH and AIS, according to the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society lung adenocarcinoma classification.19 Multiple studies have reported that the nonsolid component tended to correspond to lepidic histology and the solid component tended to correspond to invasive patterns.20-26 In the eighth edition of the TNM classification, MIA has been clinically defined as a subsolid nodule with a solid component <5 mm and pathologically defined as a lepidic adenocarcinoma with an invasive pattern <5 mm.27 A 10-year follow-up study of pure GGO showed that approximately 38% of CT-detected pure GGO were pathologically diagnosed as AIS, 40% were MIA, and 12% were lepidic-predominant invasive adenocarcinoma.28 Okubo and colleagues24 have reported that the proportion of lepidic components on pathologic diagnosis tended to be smaller than that of the

<table>
<thead>
<tr>
<th>Statement</th>
<th>Terminology</th>
<th>Definition</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subsolid nodule</td>
<td>A focal ground-glass opacity identified on computed tomography with variable solid components within which the presence of underlying pulmonary vessels or bronchial structures remain visible</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Nonsolid nodule</td>
<td>Nodule without any solid component</td>
<td>5,13-15</td>
</tr>
<tr>
<td>3</td>
<td>Part-solid nodule</td>
<td>Nodule with both ground-glass and solid components</td>
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</tr>
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<td>4</td>
<td>Heterogeneous ground-glass nodule</td>
<td>Nodule with ground-glass component and a solid portion that is exclusively in the lung window</td>
<td>16,17</td>
</tr>
<tr>
<td>5</td>
<td>Real part-solid nodule</td>
<td>Nodule with ground-glass component and a solid component present in both the lung and mediastinal windows</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Minimally invasive adenocarcinoma</td>
<td>A lepidic adenocarcinoma with an invasive pattern &lt;5 mm</td>
<td>19,27</td>
</tr>
<tr>
<td>7</td>
<td>Nodule growth (for nonsolid nodule)</td>
<td>An absolute increase in mean diameter &gt;1.5 mm or the appearance of a solid component</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>Nodule growth (for part-solid nodule)</td>
<td>An absolute increase in mean nodule or solid component diameter &gt;1.5 mm</td>
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</table>
nonsolid components on radiologic images in cT1N0M0 lung cancer, suggesting that some invasive components also present as radiological ground-glass components. These findings indicate that the nonsolid component generally corresponds to preinvasive histology, but not entirely. Moreover, recent studies found that rPSN exhibit greater invasiveness than hGGN. Ongoing controversies still remain regarding whether rPSN represents invasive adenocarcinoma without lepidic component.17,18,29

Despite being considered as an indolent subtype, approximately 20% of nonsolid nodules are found to be associated with the new appearance of a solid component on surveillance.30 Lee and colleagues31 performed long-term follow-up of subsolid nodules that had already been shown to be stable over 5 years of surveillance. They found that despite 5 years of stability, 13% of these subsolid nodules showed growth in size during continued follow-up of up to 136 months. Kakinuma and colleagues16 reported that the probability of a 2-mm growth in 5 years was 14%, 24%, and 48% for nonsolid, hGGN and rPSN, respectively. Furthermore, 5% of nonsolid nodules and 20% of hGGN developed into rPSN. Bak and colleagues32 demonstrated that CT scanning attenuation value could predict growth and development of a solid component for nonsolid nodule. Taken together, increasing CT attenuation, new appearance of a solid component, and a solid component measurable in the mediastinal window might raise the suspicion of invasive adenocarcinoma.

In 2008, Hiramatsu and colleagues13 established the criteria for the “growth of GGO” as an increase in the greatest dimension of >2 mm, an increase in the size of the solid part >2 mm, or the emergence of a new solid part of any size. In the National Lung Screening Trial (NLST), nodules with a diameter of at least 4 mm or an increase in diameter of at least 10% were considered screen positive.33 For small nodules, a 10% increase falls within the range of the 95% confidence interval. To reduce the higher false-positive rate of the NLST, the Lung-RADS protocol defined nodule growth as an increase >1.5 mm mean diameter (average of each dimension). Pinsky and colleagues35 found that the Lung-RADS protocol showed a greater specificity (87.2% vs 73.4%) but lower sensitivity (84.9% vs 93.5%) when compared with the NLST protocol. In the Dutch-Belgian lung cancer screening trial (Nederlands-Leuvens Longkanker Screenings Onderzoek [NELSON]), nodules with a relative growth of more than 25% in volume and a volume doubling time of less than 400 days were defined as positive.36 However, accumulating evidence suggests that volumetric measurement for evaluating lung nodule growth exhibits greater sensitivity but lower specificity compared with diametric measurements.37,38 Considering the clinical feasibility and potential heterogeneity of volume measuring software,39 it is recommended in this document to evaluate nodule growth by measuring mean diameter (average of longest and shortest) but not volumetric or all dimensional change in clinical practice. A measurement of 1.5 mm was chosen to maintain enough equilibrium between sensitivity and specificity of nodule growth measurement. From a clinical standpoint, inter- and intraobserver nodule measurements can be improved by comparing the thin-slice images of the current CT and the oldest comparison CT, as the longer interval of time may make changes more apparent. In addition, comparison of the edge of the nodule relative to the adjacent structures, such as vessels and airways, may also help to resolve whether growth is indeed present. Further prospective trials comparing different thresholds and measurement dimensions are still warranted.

Section 2: Recommendations for the Surveillance and Diagnosis of Subsolid Lung Nodules

**Statement 5.** CT of the chest performed for the evaluation of nonsolid nodules (pure GGO) and PSNs should be reconstructed with thin axial reformats (ideally 1 mm) to allow for accurate nodule characterization (COR: I, LOE: B-non-randomized [NR]).

CT of the chest is the primary method by which indeterminate pulmonary nodules are evaluated and surveilled. Reconstruction of a CT of the chest with thin sections has been widely accepted as best practice for the characterization of pulmonary nodules. Thicker CT reconstructions suffer from greater volume averaging of the nodule with surrounding lung parenchyma and diminish readers’ ability to accurately identify and characterize nodules.

Fischbach and colleagues40 evaluated radiologists’ ability to detect pulmonary nodules on 1.25-mm slice reconstructions as compared with 5 mm with thin-section CT resulting in greater rates of nodule detection and improved interobserver agreement among readers (k = 0.753 at 1.25 mm; k = 0.562 for 5 mm). Even when presented with the aid of a computer-aided detection (CAD) tool, thin-section CT remains beneficial for nodule detection. In a study assessing the effect of CAD on radiologists’ ability to identify subsolid and solid nodules on thin- and thick-section CT, Godoy and colleagues41 demonstrated that CAD results in the greatest improvement on nodule detection when CAD marks were viewed on thin-section CT (0.67-1.0 mm) as opposed to thick-section CT (5 mm). As methods of lung nodule detection and characterization improve, platforms such as artificial intelligence-based radiomics may play a role in the future evaluation and management of subsolid lung nodules.42

In the evaluation by Lee and colleagues22 of correlation between size of solid components of subsolid nodules on CT and invasive components of lung adenocarcinomas at histologic evaluation, CTs with reconstructions >1.25-mm reconstructions were deemed insufficient for nodule analysis. Noting a preponderance of studies, either within randomized controlled trials or prospective case series
employing the use of thin-section CT, the British Thoracic Society has recommended the use of thin-section (1.5 mm) CT for reassessment of subsolid nodules. Recognizing the effect of slice thickness on the radiologist’s ability to compare nodule characteristics across timepoints, the Fleischner Society has recommended the routine use of contiguous thin-section reconstruction (≤1.5 mm, typically 1.0 mm) when interpreting imaging as well as archiving data for future use. In the absence of thin-section CT at baseline, the Fleischner Society additionally recommends short-term follow-up with thin-section CT to provide baseline characteristics for future comparison.

Statement 6. In patients with nonsolid nodules (pure GGOs) that are ≥6 mm in size, an initial repeat CT of the chest (with thin axial reformats) at a 6-month interval is reasonable to confirm persistence of the nodule. For more concerning PSNs (such as those that are ≥50% solid or with a solid component ≥6 mm), this initial interval may be shortened (COR: IIa, LOE: B-NR).

Subsolid nodules are estimated to occur in 1.8% to 2.6% of individuals undergoing CT of the chest with prevalence as high as 9% among those undergoing lung cancer screening. The majority of subsolid nodules detected at CT are transient. In the review from Lee and colleagues of 16,777 individuals receiving low-dose CT to evaluate for lung cancer, as many as 70% of detected part solid nodules were transient. These transient subsolid nodules are attributed to infectious and inflammatory pulmonary processes and may be an even more frequent finding in the era of COVID-19. Histologic comparison with CT findings of the chest provides evidence that solid components of nodules detected at CT are closely associated with the invasive components of adenocarcinomas, with nonsolid nodules more likely to represent as AAH or AIS. However, nonsolid consistency does not preclude invasiveness, with larger size (>10.5 mm), greater and heterogeneous attenuation, irregular shape, spiculated and lobulated margins, and architectural distortion increasing the probability of an invasive component. Balancing the high prevalence of subsolid nodules with the potential risk of lung cancer, a tiered approach to follow-up is recommended. An initial follow-up at 6 months is suggested to confirm the persistence of a nonsolid nodule, precluding longer-term follow-up for patients with nodules caused by a fleeting infectious or inflammatory process. Recognizing the increased risk for an invasive component in PSNs, this initial follow-up may be shortened to 3-6 months based on level of concern for PSNs.

Statement 7. In patients with persistent nonsolid nodules (pure GGOs) that are ≥6 mm in size, radiographic surveillance in a stepwise approach with initial follow-up CT of the chest in 6 months, then 12 to 24 months for at least 5 years, may be reasonable provided the nodule remains stable in size and density. Persistent PSNs that are ≥6 mm in total size are likely appropriate to follow-up more frequently at 12-month intervals or shorter (COR: class IIb, LOE: B-NR).

After the initial follow-up CT of the chest at 6 months for pure GGOs as discussed in Statement 6, radiographic surveillance should take place every 12 to 24 months for at least 5 years. This is based on knowledge of the natural history of nonsolid nodules and evidence showing that the average period of growth for nonsolid is 3-4 years. Kobayashi and colleagues followed the course of 108 subsolid lesions (76% pure GGOs) and found that 29 lesions became larger at a median observation time of 4.2 years; all growing nodules exhibited growth within 3 years from their initial detection. Lee and colleagues observed 175 nonsolid lesions with serial CTs of the chest; the median follow-up duration was 45 months, with 26.3% of GGO lesions showing significant size increases (≥2 mm in the longest diameter) and a mean doubling time of 1041 days (2.85 years).

PSNs tend to show a greater percentage of growth as compared with nonsolid and may warrant closer observation at intervals of 12 months or shorter. This was shown in a study by Matsuguma and colleagues, where they observed 174 subsolid nodules with CTs of the chest and showed that the 2-year and 5-year cumulative percentage of growing nodules were 13% and 23% in pure GGO nodules and 38% and 55% in part solid nodules, respectively.

Statement 8. Strong consideration should be made for continued follow-up of subsolid nodules that have not changed even after 5 years. Beyond 5 years, reimaging every 2 to 4 years should be considered for at least 10 years if medically fit (COR: IIa, LOE: C-expert opinion [EO]).

There are limited data available on whether and when surveillance of subsolid nodules can be discontinued after no change in size or density has been seen after a certain period of monitoring. Although traditionally it has been considered safe to deem solid nodules benign after monitoring for 2 years without change, this is certainly too short a surveillance duration with slower-changing subsolid nodules. Although Fleischner guidelines recommend ceasing follow-up if a subsolid nodule has been stable for 5 years, the available data cast doubt on this. Cho and colleagues noted growth in 7% of 218 mostly PSNs that had been stable on imaging for 3 years. More concerning, Lee and colleagues reported on 208 primarily nonsolid nodules that had been stable for 5 years but then continued to be followed for a median of 8.2 years: 13% of the nodules grew >2 mm after the 5 years of stability, and 16% developed a solid component. Although lymph node and distant metastases are uncommon in subsolid lung cancers, increasing solid component and size contribute to worse survival outcomes compared with subsolid lesions that are resected at the AIS/MIA stage, where recurrence-free survival approaches 100% with resection. Therefore,
long-term surveillance aims to avoid overtreatment while increasing chances of offering resection within a curative time window.54

Because of the scarcity of data on the optimal duration of surveillance, decisions on when to discontinue surveillance should ultimately be made in the context of clinical factors, such as comorbidities, life expectancy, and patient preference. An 80-year-old patient with major comorbidities would be highly unlikely to die of a subcentimeter subsolid nodule that has demonstrated slow growth trajectory over 5 years. In contrast, a 50-year-old patient likely to otherwise live another 30 years should probably have any subsolid nodule followed well beyond 10 years. It is likely that a surveillance interval of 2 years or more is reasonable in these individuals, given the risks of the radiation exposure with multiple CTs over many years. The lowest-dose CT protocols that allow evaluation of solid components should be used.

**Statement 9.** In patients with subsolid nodules ≥8 mm in size and morphologic features of lobulated or spiculated nodule margins, ≥6 mm solid component, air bronchograms, or adjacent pleural or vascular changes, suspicion for invasive adenocarcinoma should be high with a resulting decrease in the surveillance interval and/or tissue sampling versus resection based on patient factors (COR: I, LOE: B-NR).

While observing subsolid nodules, the clinician needs to stay vigilant about size and morphologic changes that may point toward the development of invasive adenocarcinoma and prompt either a more aggressive surveillance strategy, tissue sampling or resection. Multiple studies have compared the morphologic features of subsolid nodules on thin-section CTs of the chest with their histopathologic results to identify predictors of invasiveness.15,44,58-59 Zhang and colleagues50 studied the radiographic characteristics of 237 subsolid lung nodules confirmed by surgical resection to be either AIS and MIA (n = 139) or invasive adenocarcinoma (n = 98). Compared with the AIS/MIA group, the invasive adenocarcinoma group exhibited larger size nodules (15.2 mm vs 11.1 mm, P = .005) with larger solid components (10.3 mm vs 6.1 mm, P = .044), greater frequency of lobulated shape and spiculated margin, abnormal pulmonary artery or vein, presence of air bronchogram, and pleural indentation.

The decision to proceed with either additional short-term surveillance, biopsy, or surgical resection should be made on the basis of a multidisciplinary discussion of best approach and the patient’s overall functional status and personal preferences.

**Statement 10.** In patients with a PSN ≥8 mm in total size with evidence of growth on surveillance studies, biopsy or limited resection (if feasible) is suggested (COR: IIa, LOE: B-NR).

Subsolid nodules <8 mm are low risk for advancing in stage beyond a highly curable lesion while under surveillance and thus surveillance is justified based on the 8-mm threshold. In addition, the smaller the nodule, the lower the reliability of any diagnostic procedure and localization during surgery. Growing, nonsolid nodules can almost certainly be safely monitored well beyond 1 cm, without advancing in stage/curability, and likely up to 2 cm.63 In contrast, growing PSNs begin to develop some (low) risk of lymph node metastasis when the solid component reaches 6 mm. One study, for example, showed the rate of nodal involvement for PSNs to be 3% when >1 cm in diameter and 14% when >2 cm.61 Pathologically, 5 mm of histologic invasion has been selected as the dividing line between “invasive” and “minimally invasive” adenocarcinoma because there begins to be some risk of metastasis >5 mm.62 In addition to the aforementioned, there are at least 3 other reasons that 8 mm is a reasonable size threshold at which to consider nonurgent diagnosis and/or intervention in a lesion that has proven it will grow: (1) the high incidence of adenocarcinoma-spectrum lesions in growing PSNs; (2) the likelihood that growing PSNs (even nonsolid nodules) 8 mm and greater are not “pseudo-tumors” that will never require treatment; and (3) the fact that as even a nonsolid nodule approaches 2 cm, the likelihood that complete resection can be achieved by a simple video-assisted thoracic surgery wedge falls. Eight millimeters is typically large enough to allow digital palpation of a peripheral nodule during video-assisted thoracic surgery—certainly of a PSN—and although resection is not an urgent matter at 8 mm, there is, in contrast, no obvious advantage to further delay when a nodule is growing, except perhaps when there are multiple nodules.

Although advancements in the reliability of needle-based diagnostic techniques for small pulmonary nodules have been considerable, there will still be only modest diagnostic success rates with 8- to 10-mm nodules. A meta-analysis of studies measuring the diagnostic accuracy of percutaneous transthoracic needle biopsy for subsolid lung lesions revealed a pooled sensitivity and specificity of 90% and 99%, respectively.63 However, a retrospective study demonstrated lower sensitivity for making a diagnosis of malignancy in subsolid lesions smaller than 2 cm compared to larger lesions (88.6% vs 95.6%).64 A recent prospective study showed the following performance characteristics of electromagnetic navigational bronchoscopic biopsy of nodules with mean 2.0 cm diameter: sensitivity, specificity, positive predictive value, and negative predictive values of 69%, 100%, 100%, and 56%, respectively.65 A retrospective study of similarly sized lung nodules suggested that adding cone beam CT and a robotic bronchoscopy platform improves sensitivity to 87.3% and negative predictive value to of 81.3%.66 These numbers, however, would clearly be substantially lower for smaller nodules and subsolid nodules,67 for which expecting negative predictive values >60% seems optimistic.
Most subsolid nodules that grow will prove to be on the adenocarcinoma spectrum. The high rate of adenocarcinoma in such suspicious lesions and the modest reliability of needle-based biopsy techniques have important implications for the most efficient and effective approach to diagnosis and management. A patient with a near-100% chance that a growing, ≥8 mm lesion is on the adenocarcinoma spectrum (e.g., a nonsmoking woman of Asian descent, or with morphologic features, as mentioned in Statement 8), in whom the lesion is positioned peripherally enough to allow wedge resection with near-certainty, should very likely undergo wedge resection without preliminary needle biopsy when that lesion becomes threatening. Segmentectomy may also be reasonable for a lesion nearing 100% diagnostic certainty on pretest probability that it is a cancer. A preliminary attempt at biopsy in such a patient merely increases cost and inconvenience, causes delay, and a false-negative biopsy may be misinterpreted as a true-negative. In contrast, a patient who is not in a group that is at high risk for malignant subsolid nodules, and/or a lesion that would require anatomic resection of multiple segments or a lobectomy, should likely undergo an attempt at bronchoscopic or transthoracic needle biopsy in order try to establish a diagnosis preresection. In these patients, the occasional identification of a specific benign diagnosis by needle biopsy will avert the need for an anatomic resection that does engender some morbidity and even rare deaths. However, the risk of a false-negative in any nonspecific “negative” biopsy result needs to be kept closely in mind; and, in that situation, resection or continued radiographic surveillance is required.

**Statement 11.** Magnetic resonance imaging (MRI) of the brain, bone scan, and positron emission tomography (PET)/CT are not indicated for preoperative evaluation of nonsolid nodules (pure GGOs) <3 cm (COR: IIa, LOE: B-NR).

Guideline-recommended preoperative work-up for lung cancers may include fluorodeoxyglucose (FDG) PET/CT, bone scanning, and MRI of the brain for staging purposes. However, in early-stage lung cancer (particularly in stage IA), the prevalence of extrathoracic metastasis at initial diagnosis varies among different studies. Subsolid early-stage lung cancer has been well defined as a clinically indolent subtype with fewer local recurrences and metastases. To be noted, recent studies have shown bone scanning and MRI of the brain had no yields for patients with subsolid-featured lung adenocarcinoma and should therefore be omitted for these patients. Zhuge and colleagues retrospectively enrolled 3392 patients with pathologically proven primary lung cancer who underwent an MRI at initial diagnosis. Brain metastasis was detected in 0.7% patients with clinical stage IA lung cancer, all of whom radiologically featured solid lesions. A prospective multicenter study investigated the necessity of preoperative bone scan for patients with cT1N0 subsolid lung cancer, and none of the 691 patients had positive bone scan results. In addition, PET/CT has limited value in discriminating between benign and malignant lesions as well as for staging in nonsolid lung nodules. In a retrospective study by Cho and colleagues, they found that in 164 cases of lung adenocarcinomas presenting as nonsolid lung nodules, PET/CT identified abnormal lymph node FDG uptake in 2 cases (1.5%), both of which were found to be benign on final pathology. These findings suggest that MRI of the brain, bone scan, and PET/CT may be low yield for nonsolid nodules (pure GGOs) <3 cm and could be omitted for these patients. Until more detailed evidence is available, PET/CT is still recommended for part-solid lung cancers per existing guidelines due to the likelihood of invasive carcinoma.

**Section 3: Surgical Intervention**

**Statement 12.** In patients medically suitable for and amenable to surgery, sublobar resection (wedge resection or segmentectomy) may be considered for peripheral subsolid lesions <2 cm (COR: IIa, LOE: B-randomized).

On the basis of lower recurrence rates and improved survival of patients who undergo lobectomy in the randomized controlled trial conducted by the Lung Cancer Study Group, limited resections have been reserved for patients with non–small cell lung cancer (NSCLC) with prohibitive medical comorbidities such as marginal pulmonary functions that preclude lobectomy. The recent publication of 2 randomized, controlled trials supporting the role of limited resections through showing a noninferiority of limited resections has changed the surgical approach for nodules ≤2 cm.

In the first of these 2 trials (JCOG0802/WJOG4607L) comparing segmentectomy to lobectomy for peripheral NSCLC ≤2 cm, the 5-year overall survival (OS) was 94.3% for segmentectomy and 91.1% for lobectomy. For OS, their Cox regression model demonstrated noninferiority and superiority for segmentectomy (hazard ratio, 0.663; 95% confidence interval, 0.474-0.927; one-sided $P < .0001$ for noninferiority). The 5-year relapse-free survival was 88.0% for segmentectomy and 87.9% for lobectomy. Importantly, the trial specified a radiographic consolidation-to-tumor ratio (CTR) >0.5 in the inclusion criteria. The CTR stratifies subsolid lesions from predominately nonsolid (CTR <0.5) to predominantly solid (CTR >0.5) to reflect the spectrum of subsolid lesions.

In the second of these 2 trials, Altorki and colleagues in the Cancer and Leukemia Group B 140503 trial similarly randomized patients with peripheral NSCLC ≤2 cm to undergo sublobar resections versus lobectomy. This study included wedge resections as well as segmentectomies. The 5-year OS was 80.3% for sublobar resection and 78.9% for lobectomy. For OS, their Cox
proportional-hazards model demonstrated noninferiority for sublobar resection. The 5-year disease-free survival (DFS) was 63.6% after sublobar resection and 64.1% after lobar resection. The DFS after sublobar resection also demonstrated noninferiority. Ultimately both studies independently concluded that their limited resections were acceptable alternatives to lobectomy for peripheral, pathologically node-negative, NSCLCs ≤2 cm.

Relevant to the discussion centering on subsolid nodules, JCOG0802/WJOG4607L trial was among a portfolio of trials that evaluated permutations of different tumor sizes and CTRs. The Cancer and Leukemia Group B 140503 study did not specify CTR in their inclusion criteria; however, from their discussion, it was possible to infer that lesions with subsolid nodules typically were not included and their results pertained more to pure solid lesions. The applicability of this study to the domain of subsolid nodules resides in the fact that pure solid lesions correlate with more aggressive lesions than those that are nonsolid or PSNs.

Among prospective single-arm and retrospective studies simply reporting outcomes associated with either wedge resections or segmentectomies for subsolid nodules, 5-year OS and recurrence-free survival (RFS) or DFS have been observed to be between 90% and 100% and 85% and 100%, respectively. For example, in the prospective single-arm study of sublobar resection for peripheral subsolid lesions with CTR <0.25 published by Suzuki and colleagues, 5-year relapse-free survival was 99.7%. Of the 314 patients included in the study, 82% had undergone wedge resection. In studies comparing limited resections with each other or with lobectomies for subsolid nodules, the reported ranges of 5-year OS and RFS for exclusively limited resections appears to range from 86% to 100% and 75% to 100%, respectively. The 5-year OS and RFS for lobectomies in these same studies have been slightly greater, although not to statistical significance ranging between 93% and 100% and 90% and 100%, respectively.

Other metrics of favorable outcomes associated with resections for subsolid nodules also include lung cancer-specific survivals that range from 95% to 100% when reported. Long-term outcomes for subsolid nodule resections offer a 10-year OS and RFS in the ranges of 70% and 90% and 61% and 97%, respectively.

In general terms, outcomes associated with resections for subsolid nodules have been more favorable, with nonsolid nodules faring the best, regardless of the resection type or other features. In the studies that have evaluated subsolid nodules along the spectrum of pure, part-solid, and solid, a common theme is that the purer the GGO, or alternatively, the less solid component that is present, the more favorable is the survival. In this regard, the refinement of CT scanner technology has led to more objective measures of subsolid nodules in predicting tumor invasiveness. In 2011, the first of several key publications arising from a prospective clinical collaboration in Japan across a number of institutions yielded the impactful observation that for tumors ≤2 cm and with a CTR <0.25, discriminating noninvasive from more invasive NSCLCs was possible. Subsequent to these findings, many have employed the CTR of either 0.25 or 0.5 for their inclusion or exclusion criteria into studies evaluating the role of sublobar resections.

Most of the contemporary scientific evidence shows that the histopathologic correlates of radiographically solid lesions are associated with more aggressive potential than the histopathologic correlates of subsolid nodules. On the basis of this knowledge, as well as data from the past 2 decades demonstrating the adequacy or equivalence of limited resections to lobectomy for subsolid nodules ≤2 cm in terms of survival, limited resections are a reasonable option. Furthermore, the data from 2 recent randomized, controlled trials that would have encompassed subsolid nodules ≤2 cm, if they were eligible to be included, strongly endorses limited resections. Therefore, when feasible limited resections are the preferred parenchymal sparing approach for subsolid nodules ≤2 cm (Table 2).

Statement 13. In patients medically suitable for and amenable to surgery, lobectomies may be considered for subsolid cancers that are: nonperipheral (central), >2 cm with a CTR >0.5, or for which adequate surgical margins cannot be obtained with a lesser resection (COR: IIb, LOE: B-NR).

Although there is substantial data supporting the use of limited resections for lesions that are ≤2 cm, the evidence supporting limited resections for lesions >2 cm is somewhat mixed. More specifically, when performed for lesions >2 cm, the role of sublobar resections may also be called into question owing to the data that may show worse outcomes associated with this subset. Using the lobectomy cohort from the Japan Clinical Oncology Group 0201 study, Asamura and colleagues reported that among patients who had adenocarcinomas >2 cm and ≤3 cm, the 5-year OS and RFSs were 87.8% and 79.9%, respectively. On the basis of size alone, this survival was inferior to the 5-year OS and relapse-free survival reported among adenocarcinomas ≤2 cm, which were 93.0% and 88.9%, respectively. In another prospective multicenter study evaluating lobectomies and limited resections of subsolid cancers inclusive of nodules ≤3 cm, larger nodule size emerged as a strong variable for recurrence.

Reports of increased recurrences and decreased RFS have suggested that for subsolid cancers ≥2 cm, a lobectomy should be considered because of a greater chance of recurrence. Other studies have shown that an increasing T descriptor, a surrogate for size, has been associated with lower OS and RFS. The need to dissect the hilar lymph nodes due to the elevated risk of their involvement with
subsolid cancers >2 cm and ≤3 cm, also has been the rationale for recommending segmentectomy over wedge resection.85 CTR >0.5 has been shown to be associated strongly with either greater recurrence rates and/or worse RFS for limited resections compared to lobectomies.83,92 Given that these studies have found inferior outcomes in subsolid nodules ≤2 cm, it is very reasonable to conclude that subsolid cancers >2 cm and with a CTR >0.5 carry a worse prognosis. Therefore, in the absence of stronger data to support the role of limited resections in subsolid cancers >2 cm and with a CTR >0.5, as well as the accumulation of data showing that a higher T descriptor is a proxy of advancing disease, lobectomy appears to be the most prudent approach over limited resection.

Statement 14. When a frozen section of the margin is positive after a sublobar resection for a subsolid cancer, a completion segmentectomy or lobectomy should be considered (COR: IIa, LOE: C-limited data).

The promising results associated with sublobar resections for subsolid cancers may be predicated on the fact that many studies either have mandated or recommended a specific margin at the time of resection.75,77-79,84 Interestingly, the use of frozen sections in achieving this margin at the time of final pathology. There are studies that have relied on frozen section analysis that have commented on the difficulty in rendering a diagnosis or assessing the time of final pathology. There are studies that have inferred that the margin appreciated is that which is found at the time of operation is less well described, and so it may be worth noting that CTR is not a proxy of advancing disease.

Table 2. Selected studies evaluating sublobar resections

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication year</th>
<th>Study type</th>
<th>N*</th>
<th>Resection type</th>
<th>Tumor Classification or CTR</th>
<th>Size</th>
<th>Survival (5-y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakao et al79</td>
<td>2012</td>
<td>Prospective</td>
<td>40</td>
<td>W+S</td>
<td>L: 26</td>
<td>Nog</td>
<td>≤2.0 cm</td>
</tr>
<tr>
<td>Cho et al65</td>
<td>2015</td>
<td>Retrospective</td>
<td>97</td>
<td>W: 71</td>
<td>≤0.25</td>
<td>≤3.0 cm</td>
<td>OS: 98.6% RFS: 100%</td>
</tr>
<tr>
<td>Yano et al76</td>
<td>2015</td>
<td>Retrospective</td>
<td>1737</td>
<td>W[S]: 643</td>
<td>1094</td>
<td>≥0.25</td>
<td>≤2.0 cm</td>
</tr>
<tr>
<td>Nishio et al73</td>
<td>2016</td>
<td>Retrospective</td>
<td>190</td>
<td>S: 118</td>
<td>&gt;0.25</td>
<td>≤2.0 cm</td>
<td>OS: 86.4% RFS: 75.4%</td>
</tr>
<tr>
<td>Sagawa et al77</td>
<td>2017</td>
<td>Retrospective</td>
<td>53</td>
<td>W: 39</td>
<td>≤0.2</td>
<td>≤2.0 cm</td>
<td>OS: 98.1% DFS: 98.1%</td>
</tr>
<tr>
<td>Ha et al76</td>
<td>2018</td>
<td>Retrospective</td>
<td>128</td>
<td>W: 40</td>
<td>≤0.25</td>
<td>≤2.0 cm</td>
<td>OS: 100% DFS: 100%</td>
</tr>
<tr>
<td>Ye et al81</td>
<td>2018</td>
<td>Retrospective</td>
<td>831</td>
<td>W[S]: 474</td>
<td>278</td>
<td>0 ≤3 cm</td>
<td>OS: 99.8% DFS: 99.4%</td>
</tr>
<tr>
<td>Suzuki et al78</td>
<td>2022</td>
<td>Prospective</td>
<td>333</td>
<td>W[S]: 264</td>
<td>≤0.25</td>
<td>≤2.0 cm</td>
<td>OS: 99.4% DFS: 99.7%</td>
</tr>
<tr>
<td>Li et al79</td>
<td>2022</td>
<td>Retrospective</td>
<td>125</td>
<td>W[S]</td>
<td>L: 78</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>Saji et al83</td>
<td>2022</td>
<td>RCT</td>
<td>1106</td>
<td>S: 552</td>
<td>≤2.0 cm</td>
<td>OS: 94.3% DFS: 88.0%</td>
<td></td>
</tr>
<tr>
<td>Altorki et al74</td>
<td>2023</td>
<td>RCT</td>
<td>697</td>
<td>W[S]</td>
<td>L: 554</td>
<td>≤2.0 cm</td>
<td>OS: 80.3% DFS: 87.9%</td>
</tr>
</tbody>
</table>

CTR, Consolidation-to-tumor ratio; W, wedge resection; S, segmentectomy; L, lobectomy; Nog, Noguchi A and B types at study enrollment but included C type pathologically (correlating with bronchoalveolar carcinoma); OS, overall survival; RFS, recurrence- or relapse-free survival; DFS, disease-free survival; JCOG, Japan Clinical Oncology Group; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; RCT, randomized controlled trial; NAS, not available or specified; CALGB, Cancer and Leukemia Group B. *Resected patients from larger eligible cohort. | Size based on eligibility criteria. | Number of nodules; number in parentheses reflects actual number of patients. | Value represents weighted average as survival reported for AIS and MIA individually. | Methods indicate "pure ground-glass opacities" not eligible.
confirm the attainment of a minimum 5-mm margin. If the frozen section confirmed a NSCLC diagnosis or revealed an insufficient margin, then it warranted conversion of a diagnostic wide wedge resection to either a segmentectomy or lobectomy. This paradigm, 1.5% underwent a conversion to a segmentectomy and 3% patients underwent a conversion to a lobectomy. For other studies in which positive margins or close margins are observed, the recommendation or practice to achieve a better margin has been variable and has included a wedge to additional wedge, segmentectomy, or lobectomy as well as a wedge or segmentectomy to a lobectomy. 75,77,79,83,84,94-96

The favorable outcome associated without an additional resection may reflect the indolent biology of some subsolid cancers. There are investigations that have demonstrated that among patients with subsolid nodules with a CTR ≤ 0.5, that margin distance is not predictive for recurrences. 93,97 Moon and colleagues 97 observed, however, that among patients who had a CTR > 0.5 5-year RFS was 79.6% in the group with a > 5 mm surgical margin but 24.2% in the group with a ≤ 5 mm surgical margin, which was significantly different than the 100% survival noted among subsolid nodules with a CTR ≤ 0.5.

Cumulatively, these types of findings imply that frozen section analysis may inform the thoracic surgeon how to proceed but these data are yet to be definitive. If the frozen section is performed and does show a positive margin, adhering to routine surgical oncology principles in resecting this margin is the best maneuver. In the absence of data indicating the preferred resection, a completion anatomic resection is recommended. This presumes that the patient is physiologically fit to undergo an extended resection, and does not apply to patients who are limited to sublobar resections due to poor lung function.

**Statement 15.** When the final pathology of the resected subsolid cancer demonstrates AIS or minimally invasive adenocarcinoma, surveillance may occur annually (COR: IIb, LOE: C-EO).

Whether in the isolated or multifocal subsolid nodule setting, the overall recurrence rates of adenocarcinoma in the context of previously resected subsolid nodules have been reported to range from 1.4% to 26.7%. 89,98-100

There is 10-year follow-up data showing that the secondary primary lung cancer rate is 6.4% occurring in patients who have had previous resections for what was ultimately found to be AIS and minimally invasive adenocarcinomas. 78

Recurrence appears to have a relationship with CTR with greater CTRs being associated with increased rates of recurrence, decreased RFS, and faster time to recurrence. 78,98 In general, it appears that when AIS, minimally invasive adenocarcinomas, or lepidic predominant adenocarcinomas recur, they do so over a longer period of time and, thus, a 5-year window may not serve as the appropriate timeframe in which surveillance should cease. 78,92,94,101 The paucity of data on postoperative surveillance pertaining to isolated subsolid nodules that are resected may be limited and possibly driven by the narrative that at 5 years a patient is deemed surgically “cured” and, thus, additional follow-up is no longer required.

Presently, there is no universally accepted protocol for the postoperative surveillance associated with the resection of subsolid cancers specifically. In studies describing their follow-up, the ones that were conducted in a prospective fashion and a few retrospective ones employed institutionally modified versions of accepted guideline concordant follow-up. 68,81,83,88,93,95,96 Ultimately, the entirety of these various protocols has appeared adequate. Resected subsolid lesions that are proven to be invasive on final pathology should follow pre-existing general guidelines for lung cancer surveillance that recommend CT of the chest every 6 months for at least the first 2 years after surgery, followed by annual imaging. 68,102,103 Because of the low incidence of recurrence associated with adenocarcinomas in situ and minimally invasive adenocarcinomas as well as the indolent and slow-growing nature of such lesions, starting with a longer initial interval of annual scans—instead of every 6 months—may be considered when final pathology confirms the diagnosis. For patients with multifocal subsolid lesions, the postoperative surveillance strategy should include the surveillance requirements of the remaining nodules, per recommendations in Section 2 of this document.

**Section 4: Managing Multiple Subsolid Lung Nodules**

**Statement 16.** When biopsy is indicated in patients with multiple subsolid nodules, the biopsy should target the dominant lesion (COR: IIa, LOE: C-EO).

Multiple subsolid nodules are an increasingly frequent finding as a result of CT screening for lung cancer, as incidental findings from other imaging, or as part of the presentation with a solid lung nodule or proven lung cancer. The NELSON trial showed that 51.5% of participants had 1 nodule, 23.6% had 2 nodules, 10.4% had 3 nodules, 5.6% had 4 nodules, and 8.9% had more than 4 nodules. 104 In 20% to 30% of subsolid nodules that were resected, they were found to be accompanied by multiple other smaller intrapulmonary subsolid nodules. 105,106

Multiple subsolid nodules, or synchronous subsolid nodules, are defined as 2 or more nodules that are present in the same patient at the same time. It is important to rule out infection or other benign causes, such as inflammatory granulomas. The National Comprehensive Cancer Network (NCCN) suggests that many nonsolid nodules discovered incidentally may resolve. 107 In the context of lung cancer, synchronous lung nodules have been reported to occur in 3.7% to 8% of patients. 108

Kim and colleagues 109 reported that in 23 patients who had multiple pure GGOs, after resection of the dominant lung cancer, postoperative surveillance CT showed that at
Sato and colleagues showed that for patients with multifocal subsolid nodules, at a median follow-up of 45.5 months, progression of the nodules was observed in only 32% of patients up to 36 months. These findings suggest that many cases of multiple subsolid nodules are indolent in their behavior.

The Fleischner Society recommends for multiple subsolid nodules, where there is at least 1 nodule that is larger than 6 mm, management decisions should be based on the most suspicious lesion. If the nodules persist on repeat CT after 3 to 6 months, then the possibility of multiple primary adenocarcinomas should be considered. Where there are multiple subsolid lesions 6 mm or larger, the dominant lesion—defined as the most suspicious nodule by radiographic features (which may not necessarily be the largest in size)—should guide management.

For the 8th edition of the lung cancer TNM classification, the International Association for the Study of Lung Cancer subcommittee made recommendations on lung cancer presenting as multiple subsolid nodules. Multifocal subsolid/lepidic lung adenocarcinoma should be classified by the T category of the lesion with the highest T. Nodule size is determined by the largest diameter of the solid component (by CT) or the invasive component (under the microscope). The authors also suggest that pure GGOs smaller than 5 mm not be taken into account, and that tumors that are almost completely solid or invasive (ie, have a ground glass or lepidic component of <10%) not be classified under this rubric.

More recently, Hattori and colleagues showed that in patients with “multifocal GGOs,” defined as lesions showing a GGO component for all tumors, they had significantly better 5-year OS than patients with nonmultifocal GGOs. They suggested that the presence of a GGO component has the ability to distinguish the survival even for multiple lung cancers, and proposed further investigations to address the revision of T variable of multiple lung cancers considering a presence of GGO component.

**Statement 17.** In patients with multiple subsolid nodules, combinations of local therapies may be considered. In cases in which multiple lesions require treatment and it is not feasible to treat all with a surgical approach, resection may be performed for the dominant lesion(s) and/or for lesion(s) amenable to sublobar resection, while nonsurgical treatment may be offered to the remaining subsolid nodules (COR: IIb, LOE: C-EQ).

Practical challenges regarding combined treatment strategies for multiple subsolid nodules include (1) the difficulty in determining whether one is dealing with multiple primary lung cancers or intrapulmonary metastases before surgery, especially when the lesions have similar histology; and (2) information on the risks of recurrence and factors influencing survival are limited.

Distinguishing between intrapulmonary metastasis and synchronous multiple cancers is important for management. Traditionally, clinicians have used the Martini and Melamed criteria. However, advances in modern pathology and molecular techniques have greatly improved our understanding of the clonal origin of multiple primary lung cancer (MPLC) beyond these empirical criteria.

Liu and colleagues investigated the epidermal growth factor receptor (EGFR) mutational profiles in 159 multiple subsolid lesions from 78 patients and demonstrated great variety. Of the 38 paired lesions in patients harboring EGFR mutation, the discordance rate of EGFR mutation was 92.1%, suggesting different clonal origin of the lesions. Earlier studies such as this one which utilize gene panels containing a few oncogenic/tumor-suppressor genes (usually 1 to 5 genes) and chromosome alterations in MPLC as the focus, were far from enough for profiling the MPLC genome. The precise differentiation between MPLC and IPM is one of the driving forces of the genomic exploration of MPLC. With the widespread use of next-generation sequencing, more precise determination of the clonal relationship between multiple primary lung cancer can be made.

Li and colleagues reported a series in which 154 subsolid nodule samples from 120 treatment-naïve Chinese patients were submitted to whole-exome sequencing. The authors showed that multicentric origin was predominant, although they also detected early metastatic events among multifocal subsolid nodules. Genomic profiling information has superseded the traditional clinicopathologic criteria of MPLC.

The NCCN guidelines recommend patients with multiple nodules be evaluated in a multidisciplinary setting including pathologists, radiologists, pulmonologists, surgeons, radiation oncologists and medical oncologists. Depending on the individual cases, these discussions may rely on radiographic data with or without genomic data (which may not be available preoperatively for each nodule) to interpret the nature of multiple lesions and make recommendations for the management of multiple synchronous cancers. Lesions at low risk of becoming symptomatic can be observed (eg, small subsolid nodules with slow growth). However, for lesions that show accelerating growth, increasing solid component or increasing FDG uptake, even while small, should be considered for treatment. Lung-sparing resection is preferred, but the number of target lesions, their distribution and institutional expertise should guide individual treatment planning.

**Surgery for Multiple Subsolid Nodules**

Surgical strategies including resection extent and nodule selection should comprehensively integrate several factors such as radiologic nodule features, nodule location, intraoperative frozen section diagnosis, and patients’ pulmonary function. Zhang and colleagues proposed that surgical
resection for synchronous multiple lung adenocarcinoma should be considered for all solid and subsolid nodules suspected to be malignant, easily accessible ipsilateral pure GGO, and contralateral subsolid nodules with increasing size or solid component during the follow-up period. Even for patients for whom only a dominant nodule can be resected, they should not be denied resection because of the remaining unresected subsolid nodules. Gao and colleagues\textsuperscript{121} reported that 15.7\% of patients with unresected subsolid nodules after resection of a pN0 dominant tumor underwent subsequent intervention for a progressing subsolid nodule. However, neither growth of subsolid nodules, nor the need for an intervention, negatively influenced survival.\textsuperscript{121}

For patients with synchronous multiple primary lung cancers that were not within the same lobe, lobectomy combined with a limited resection (wedge resection or segmentectomy) might be sufficient for survival benefit and lung parenchyma and lung function preservation.\textsuperscript{122}

### Nonsurgical Treatment for Multiple Subsolid Nodules

Some patients—with single or multiple subsolid nodules—may not be suitable to undergo surgical resection because of poor cardiopulmonary reserve, other medical comorbidities, advanced age, previous lung resection, or because the patient refuses to undergo surgery. In the specific scenario of multiple nodules requiring treatment, some cases may involve more nodules than can be treated with surgery alone, and alternative local therapies may be considered in addition to surgery as part of a complete treatment plan. Just as for surgical planning, integrating factors such as nodule size and location, as well as patients’ pulmonary function, is critical with nonsurgical treatment approaches to multiple nodules and requires the input of multidisciplinary expertise.

SBRT is a commonly used alternative for local treatment of medically inoperable early-stage NSCLC. Eriguchi and colleagues\textsuperscript{123} reported that 24 patients were treated with SBRT for operable early-stage NSCLC with subsolid nodules. With a median follow-up time of 40 months, cause-specific survival and OS rates at 3 years were 100\% and 100\%, respectively. No grade 4 or 5 radiation pneumonitis occurred. Tomita and colleagues\textsuperscript{124} undertook a meta-analysis of surgery versus SBRT in patients with clinical stage I NSCLC and performed propensity score matching including a balanced ratio of subsolid nodules between surgery and SBRT groups, with 120 patients in each arm. The median follow-up time of the surgery and SBRT groups were 58 months and 75 months, respectively. The results showed that the OS and progression-free survival (PFS) of the surgery group were slightly better than those of the SBRT group, but there was no significant difference in survival rates between them.\textsuperscript{124}

Thermal ablation has been used to treat early-stage lung cancer. Most clinical reports focus on radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation.\textsuperscript{125-128} The published literature on the use of thermal ablation on subsolid nodules is limited and consists of a small number of clinical series. Kodama and colleagues\textsuperscript{129} reported that lung RFA was performed on 33 patients with 42 subsolid lung tumors with >50\% GGO components. The OS and cancer-specific survival rates were 96.4\% and 100\% at 3 years and 96.4\% and 100\% at 5 years. Yang and colleagues\textsuperscript{130} reported a pilot study in which 51 patients with lung adenocarcinoma subsolid lesions received a total of 52 percutaneous CT-guided MWA sessions. The 3-year local, PFS, cancer-specific survival, and OS were 98\%, 100\%, and 96\%, and technical success rate was 100\%. There were no deaths.\textsuperscript{130} Liu and colleagues\textsuperscript{131} reported cryoablation of 19 subsolid nodules in 14 patients, and all nodules were completely ablated within the 24 months median follow-up period. Technical success rate was 100\%, without cryoablation procedure-related death.

Huang and colleagues\textsuperscript{132} reported one of the largest ablation series, where 33 patients with 103 subsolid nodules underwent a total of 66 percutaneous CT-guided MWA sessions. The median follow-up period of all patients was 18.1 months. The rates of 3-year local PFS and OS were 100\% and 100\%, respectively. The technical success rate was 100\%, without MWA procedure-related death.\textsuperscript{132}

Liu and colleagues\textsuperscript{133} reported a case series of 87 subsolid pulmonary adenocarcinomas in 48 patients, in whom there were 8 cases of surgery combined with thermal ablation. These were done either as a 1-stage operation (2 cases of wedge resection plus thermal ablation and 1 case of thermal ablation plus lobectomy); or as 2-stage (3 cases of lobectomy then thermal ablation, 1 case of wedge resection plus wedge resection then thermal ablation, and 1 case of wedge resection then thermal ablation using either RFA or microwave ablation). The authors found that combining surgery and thermal ablation is a safe and effective treatment option for multifocal subsolid adenocarcinoma. Thermal ablation may expand the indications for hybrid surgery. However, further studies on how to combine these 2 methods are required.\textsuperscript{133}

### DISCUSSION

The diagnosis and treatment paradigms for patients with subsolid lung nodules have changed considerably over the past decades. A substantial amount of literature underscores that lung cancer presenting as subsolid nodules define a special clinical subtype with excellent long-term prognosis and a unique natural course for some patients. Resection of early-stage lung adenocarcinoma can truly improve patients’ life expectancy, which is not lead-time bias. Previous studies have demonstrated that the 5-year, and even 10-year,
RFS associated with surgically resected lung adenocarcinoma featured as radiological pure-GGO or pathologic AIS/MIA was 100%. In addition, sublobar resection may be sufficient for GGO-predominant lung adenocarcinomas. Thus, early detection followed by resection for small ground-glass–dominant nodules can be considered an efficient and effective curative-intent treatment approach. Despite this perspective, the overdiagnosis and/or overtreatment of subsolid nodules remains a major concern. This writing group sought to create a set of evidence-based recommendations aimed at striking a balance between meaningful therapy and overdiagnosis/overtreatment for subsolid lung nodules.

The topics covered in this document were developed on the basis of the literature search results and the expertise of the authors. However, there are important aspects of care for subsolid lung cancers that were not included but certainly deserve attention and require further research. One example is whether nonsurgical local treatment strategies, such as stereotactic radiotherapy or image-guided ablation therapy, can be considered equivalent treatments for subsolid lung cancers for patients with a single nodule who would otherwise be considered surgical candidates. The results of prospective randomized trials such as the Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy (VALOR) may help to answer this question for stage I lung cancers in general. Another important clinical question is whether the extent of lymph node dissection should be modified depending on the subsolid nature of a lung cancer. The NCCN guidelines as well as the American College of Surgeons Committee on Cancer state that all early-stage lung cancers undergoing resection should also undergo lymph node dissection that samples at least three N2 stations, as well as one N1 station. Although subsolid lung cancers are associated with less risk of lymph node metastases, there is a need for quality data to clarify whether there should be specific recommendations for a selective lymph node dissection or even omission of lymph node dissection in certain cases (for example, AIS/MIA). Clinical trials are underway to answer these important questions. In addition, the expanding roles for neoadjuvant and adjuvant therapies will require future elucidation of the role of biomarker testing in the early spectrum of lung adenocarcinoma commonly associated with subsolid lung lesions.

Our work provides a basic framework for the approach to a majority of patients with subsolid nodules. Future clinical and translational research will need to identify novel, noninvasive methods of discriminating benign from malignant subsolid nodules and predicting aggressive pathologic features. In addition, international, multicenter clinical trials will be important to further evaluate the applicability of current management strategies in clinical practice worldwide. However, it is difficult to conduct randomized controlled trials, given the excellent prognosis of lung adenocarcinoma manifesting as subsolid nodules, which ironically contributes to the relatively low LOE required to achieve consensus. Nevertheless, by improving our understanding of subsolid nodules with unremitting efforts, we hope to prioritize the well-being and quality of life of patients with subsolid nodules.

**Conflict of Interest Statement**

A full list of author’s disclosures is provided in Appendix E1.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** non–small cell lung cancer, subsolid, ground-glass opacity, lung nodule, surveillance, surgical strategy
### APPENDIX E1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

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- **#19-000133. Agency: Edwards Lifesciences | $11,673 total (to date) date: June 17, 2019-8/2023. Title: multicenter trial of congenital pulmonic valve dysfunction studying the SAPIEN 3 interventional THV with the Alterra adaptive prestent. PIs: Jamil Aboulhosn (UCLA site). Role: co-investigator (UCLA site). Description: clinical trial evaluating the SAPIEN 3 transcatheter valve. Grant/trial number: 2r01hl127153-06. Agency: National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI) | $1,790,532 total. Date: 8/2021-3/2025. Title: Expanding on a new paradigm for MRI in pediatric congenital heart disease. PIs: Paul Finn, MD, and Kim-Lien Nguyen, MD. Role: co-investigator. Description: improving the cardiac MRI framework to develop advanced anatomical and hemodynamic modeling techniques for complex congenital heart disease. Completion of the project will result in clinical deployment of new MRI pulse sequences, image acquisition and reconstruction strategies, and experimental and computational modeling methods. Grant/trial number: r01eb031993-01a1. Agency: NIH/NIBIB | $1,634,824 total. Date: 9/2022-5/2026. Title: Computational toolkit for normalizing the impact of CT acquisition and reconstruction on quantitative imaging features. PI: Hsu, W. Role: co-investigator. Description: this project investigates the effects of varying CT parameters on image-derived features and uses that information to identify optimal techniques to mitigate their effects in a task-dependent manner. Completed awards grant/trial number: r01hl131975. Agency: NIH/NHLBI | $237, 111 total (to date). Date: April 01, 2019-March 31, 2020, with 1 y no-cost extension. Title: validating cardiac MRI biomarkers and genotype-phenotype correlations for DMD. PI: Ennis D. Role: co-investigator. Description: to define the precision and reproducibility of several diagnostic cardiac MRI biomarkers obtained during a fast, free-breathing cardiac MRI exam for boys with Duchenne muscular dystrophy (DMD); and to define the cardiac-specific genotype-phenotype |
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Chen et al. Thoracic The Journal of Thoracic and Cardiovascular Surgery Volume Number 17.e8

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| biomarkers obtained during a fast, free-breathing cardiac MRI exam for boys with Duchenne Muscular Dystrophy (DMD); and to define the cardiac-specific genotype-phenotype correlation via outlier analysis. Grant/trial number: R01CA210360 Agency: NIH/NCI | $1,646,404 total Date: September 20, 2016-March 31, 2021 Title: Molecular & Imaging Biomarkers for Early Lung Cancer Detection in the Setting of Indeterminate Pulmonary Nodules PIs: Aberle DR, Lenburg M Role: Co-investigator Description: This proposal will develop and validate multiparametric diagnostic models of lung cancer in the broader landscape of all at-risk individuals with indeterminate pulmonary nodules in the range of intermediate risk of 6-25 mm. Grant/trial number: R56EB031993-01 Agency: NIH/NHBIB | $408,425 total Date: 2021-2022 Title: Computational Toolkit for Normalizing the Impact of CT Acquisition and Reconstruction on Quantitative Imaging Features PI: Hsu, W Role: Co-investigator Description: This project investigates the effects of varying CT parameters on image-derived features and uses that information to identify optimal techniques to mitigate their effects in a task-dependent manner. Clinical Trial Consultation Title: Metha Fibrogen 093 Description: A Phase 3, Randomized, Double-Blind, Trial of Pamerelumab (PG-3019) or Placebo in Combination with Systemic Corticosteroids in Subjects with Late Ambulatory to Non-ambulatory Duchenne Muscular Dystrophy (DMD); (through Medqia) Role: Chair BIRC (Blinded Independent Review Committee) | (Continued)
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**Reviewer relationships with industry and other entities**

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