The 2023 American Association for Thoracic Surgery (AATS) Expert Consensus Document: Management of subsolid lung nodules

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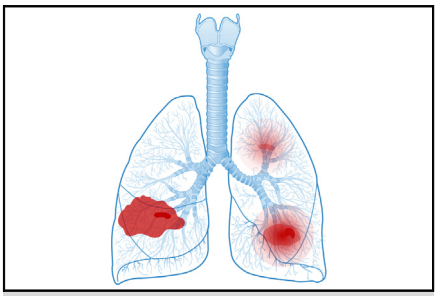
ABSTRACT

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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Abbreviations and Acronyms

AAH = atypical adenomatous hyperplasia
AATS = American Association for Thoracic Surgery
AIS = adenocarcinoma in situ
CAD = computer-aided detection
COR = classification of recommendation
CT = computed tomography
CTR = consolidation-to-tumor ratio
DFS = disease-free survival
EO = expert opinion
EGFR = epidermal growth factor receptor
FDG = fluorodeoxyglucose
GGO = ground-glass opacity
hGGN = heterogeneous ground-glass nodule
LOE = level of evidence
MIA = minimally invasive adenocarcinoma
MPLC = multiple primary lung cancer
MRI = magnetic resonance imaging
MWA = microwave ablation
NCCN = National Comprehensive Cancer Network
NLST = National Lung Screening Trial
NR = nonrandomized
NSCLC = non–small cell lung cancer
OS = overall survival
PET = position emission tomography
PFS = progression-free survival
PICO = patient intervention comparison outcome
PSN = part-solid nodule
RFA = radiofrequency ablation
RFS = recurrence-free survival
rPSN = real part-solid lung nodule
SBRT = stereotactic body radiation therapy

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 preresection 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

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FIGURE 1. Class of recommendation and level of evidence guidelines. American College of Cardiology/American Heart Association recommendation system: applying Class of Recommendation and Level of Evidence to clinical strategies, interventions, treatments, or diagnostic testing in patient care (updated May 2019). Reprinted with permission, 2016 American Heart Association, Inc. https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines/tables/applying-class-of-recommendation-and-level-of-evidence and Halperin and colleagues.[10]

recommendation (COR), and determined the level of evidence (LOE) according to guidance from AATS and Grading of Recommendations Assessment, Development and Evaluation approaches[7-9] (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

a group of external reviewers were required to review, and revise the document.

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 colleagues[24] have reported that the proportion of lepidic components on pathologic diagnosis tended to be smaller than that of the

TABLE 1. Terminology summary for subsolid lung nodules

Statement	Terminology	Definition	Ref.
1	Subsolid nodule	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	12
2	Nonsolid nodule	Nodule without any solid component	5,13-15
2	Part-solid nodule	Nodule with both ground-glass and solid components	
2	Heterogeneous ground-glass nodule	Nodule with ground-glass component and a solid portion that is exclusively in the lung window	16,17
2	Real part-solid nodule	Nodule with ground-glass component and a solid component present in both the lung and mediastinal windows	18
3	Minimally invasive adenocarcinoma	A lepidic adenocarcinoma with an invasive pattern <5 mm	19,27
4	Nodule growth (for nonsolid nodule)	An absolute increase in mean diameter >1.5 mm or the appearance of a solid component	35
4	Nodule growth (for part-solid nodule)	An absolute increase in mean nodule or solid component diameter >1.5 mm	

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 remains 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 colleagues[31] 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 colleagues[16] 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 colleagues[32] 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 colleagues[33] 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.[34] For small nodules, a 10% increase falls within the range of the 95% confidence interval. To reduce the high 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 colleagues[35] 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-nonrandomized [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 colleagues[40] 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 colleagues[41] 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 colleagues[22] 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.[43] 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.[14] 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[31] with prevalence as high as 9% among those undergoing lung cancer screening.[15,44] The majority of subsolid nodules detected at CT are transient. In the review from Lee and colleagues[45] 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.[46] 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,[22] 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.[47] 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.[48,49] Kobayashi and colleagues[48] 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[49] 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,[50] 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[51] noted growth in 7% of 218 mostly PSNs that had been stable on imaging for 3 years. More concerningly, Lee and colleagues[31] 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,[52] 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.[53] 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.[15,44,55-59] Zhang and colleagues[59] 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.[60] 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 (eg, 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.[68] 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.[3] 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[69] 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.[70] 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,[71] 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.[72] 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.[73,74]

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.[73] 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[74] 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.[74] 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.[73] 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.[74] 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.[75-80] For example, in the prospective single-arm study of sublobar resection for peripheral subsolid lesions with CTR <0.25 published by Suzuki and colleagues,[78] 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.[78,81-84] 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.[77,81] Longer-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.[79,83,84]

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.[82] 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.[85-87] 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.[21] 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.[75-78,82,88,89]

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).[73-79,81-84]

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[21,90] 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.[91]

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.[88,91] Other studies have shown that an increasing T descriptor, a surrogate for size, has been associated with lower OS and RFS.[76,88] The need to dissect the hilar lymph nodes due to the elevated risk of their involvement with

TABLE 2. Selected studies evaluating sublobar resections

Study	Publication year	Study type	N*	Resection type		Tumor Classification or CTR	Tumor Size†	Survival (5-y)	
Nakao et al[84]	2012	Prospective	40	W+S|L:	26|14	Nog	≤2.0 cm	OS: 100%	RFS: 100%
Cho et al[75]	2015	Retrospective	97	W:	71	≤0.25	≤3.0 cm	OS: 98.6%	RFS: 100%
				W:	26	>0.25	≤3.0 cm	OS: 95.5%	RFS: 85.0%
Yano et al[76]	2015	Retro	1737	W|S:	643|1094	≤0.25	≤2.0 cm	OS: 96.7%	DFS: 96.5%
						>0.25	≤2.0 cm	OS: 92.7%	DFS: 88.2%
Nishio et al[83]	2016	Retrospective	190	S:	118	>0.5	≤2.0 cm	OS: 86.4%	RFS: 75.4%
				L:	72			OS: 93.0%	RFS: 90.3%
Sagawa et al[77]	2017	Retrospective	53	W:	39	≤0.2	≤2.0 cm	OS: 98.1%	DFS: 98.1%
				S:	14				
Ha et al[82]	2018	Retrospective	128	W:	40	≤0.25	≤2.0 cm	OS: 100%	DFS: 100%
				S:	20			OS: 100%	DFS: 100%
				L:	66			OS: 100%	DFS: 92.7%
Ye et al[81]	2018	Retrospective	831‡ (736)	W|S|L:	474|89|278	0	≤3.0 cm	OS: 99.8%	RFS: 99.4%
						0< and ≤0.5		OS: 97.8%	RFS: 94.3%
						0.5< and ≤1.0		OS: 98.2%	RFS: 90.0%
Suzuki et al[78] JCOG0804 WJOG4507L	2022	Prospective	333	W|S|L:	264|58|1	≤0.25	≤2.0 cm	OS: 99.4%	RFS: 99.7%
Li et al[79]	2022	Retrospective	125	W|S|L:	78|1|46	AIS/MIA	≤3.0 cm	OS: 97.5%§	RFS: 100%
Saji et al[73] JCOG0802 WJOG4607L	2022	RCT	1106	S:	552	NAS	≤2.0 cm	OS: 94.3%	RFS: 88.0%
				L:	554			OS: 91.1%	RFS: 87.9%
Altorki et al[74] CALGB140503	2023	RCT	697	W|S:	201|129	NAS‖	≤2.0 cm	OS: 80.3%	DFS: 63.6%
				L:	357		≤2.0 cm	OS: 78.9%	DFS: 64.1%

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.

subsolid cancers >2 cm and ≤3 cm, also has been the rationale for recommending segmentectomy over wedge resection.[88] 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 operation is less well described, and so it may be inferred that the margin appreciated is that which is found 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 margin because of the well-differentiated nature of the adenocarcinomas that present as subsolid nodules.[75,94]

No clear standard for surgical margins has been established for subsolid cancer resections. Some have reported striving for a specific distance whereas other have simply reported achieving a clear margin. Suzuki and colleagues[78] mandated frozen section analysis for most of their patients to achieve histologic confirmation of their disease to

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. In 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 $\leq$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 $\leq$5 mm surgical margin, which was significantly different than the 100% survival noted among subsolid nodules with a CTR $\leq$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 re-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.[79]

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.[76,98] 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.[79,84,94,101] 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

a median follow up of 40.3 months, the remaining unresected GGOs did not change in size or radiologic features. Sato and colleagues[110] showed that for patients with multiple 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.[14]

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.[111]

More recently, Hattori and colleagues[112] 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 lesions(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-EO).

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.[111,113]

Distinguishing between intrapulmonary metastasis and synchronous multiple cancers is important for management. Traditionally, clinicians have used the Martini and Melamed criteria.[114] 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[115] 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.[116] With the widespread use of next-generation sequencing, more precise determination of the clonal relationship between multiple primary lung cancer can be made.[117-119] Li and colleagues[120] 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.[14]

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[113] 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[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.[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.[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[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[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.[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.[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[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[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.[130] Liu and colleagues[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[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.[132]

Liu and colleagues[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.[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%.[28,79,134] In addition, sublobar resection may be sufficient for GGO-predominant lung adenocarcinomas.[78] 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.[135] 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.[136,137] 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.[138-140] 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.

References

1. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382(6):503-513.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.
3. Ye T, Deng L, Wang S, et al. Lung adenocarcinomas manifesting as radiological part-solid nodules define a special clinical subtype. *J Thorac Oncol*. 2019;14(4):617-627.
4. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 suppl):e93S-e120S.
5. 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(1):304-317.
6. Zhang Y, Fu F, Chen H. Management of ground-glass opacities in the lung cancer spectrum. *Ann Thorac Surg*. 2020;110(6):1796-1804.
7. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311(7001):376-380.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
9. Bakaeen FG, Svensson LG, Mitchell JD, Keshavjee S, Patterson GA, Weisel RD. The American Association for Thoracic Surgery/Society of Thoracic Surgeons position statement on developing clinical practice documents. *J Thorac Cardiovasc Surg*. 2017;153(4):999-1005.
10. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system. *Circulation*. 2016;133(14):1426-1428.
11. Humphrey-Murto S, Varpio L, Wood TJ, et al. The use of the Delphi and other consensus group methods in medical education research: a review. *Acad Med*. 2017;92(10):1491-1498.
12. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722.
13. Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol*. 2002;178(5):1053-1057.
14. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*. 2017;284(1):228-243.
15. Yankelevitz DF, Yip R, Smith JP, et al. CT screening for lung cancer: nonsolid nodules in baseline and annual repeat rounds. *Radiology*. 2015;277(2):555-564.
16. Kakinuma R, Noguchi M, Ashizawa K, et al. Natural history of pulmonary subsolid nodules: a prospective multicenter study. *J Thorac Oncol*. 2016;11(7):1012-1028.

17. Yin J, Xi J, Liang J, et al. Solid components in the mediastinal window of computed tomography define a distinct subtype of subsolid nodules in clinical stage I lung cancers. *Clin Lung Cancer*. 2021;22(4):324-331.
18. Zhang Z, Zhou L, Min X, et al. Long-term follow-up of persistent pulmonary subsolid nodules: natural course of pure, heterogeneous, and real part-solid ground-glass nodules. *Thoracic Cancer*. 2023;14(12):1059-1070. https://doi.org/10.1111/1759-7714.14845
19. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol*. 2011;6(2):244-285.
20. Goo JM, Park CM, Lee HJ. Ground-glass nodules on chest CT as imaging biomarkers in the management of lung adenocarcinoma. *AJR Am J Roentgenol*. 2011;196(3):533-543.
21. Suzuki K, Koike T, Asakawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). *J Thorac Oncol*. 2011;6(4):751-756.
22. Lee KH, Goo JM, Park SJ, et al. Correlation between the size of the solid component on thin-section CT and the invasive component on pathology in small lung adenocarcinomas manifesting as ground-glass nodules. *J Thorac Oncol*. 2014;9(1):74-82.
23. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Oncological characteristics of radiological invasive adenocarcinoma with additional ground-glass nodules on initial thin-section computed tomography: comparison with solitary invasive adenocarcinoma. *J Thorac Oncol*. 2016;11(5):729-736.
24. Okubo Y, Kashima J, Teishikata T, et al. Prognostic impact of the histologic lepidic component in pathologic stage IA adenocarcinoma. *J Thorac Oncol*. 2022;17(1):67-75.
25. Kudo Y, Matsubayashi J, Saji H, et al. Association between high-resolution computed tomography findings and the IASLC/ATS/ERS classification of small lung adenocarcinomas in Japanese patients. *Lung Cancer*. 2015;90(1):47-54.
26. Roberts JM, Greenlaw K, English JC, Mayo JR, Sedlic A. Radiological-pathological correlation of subsolid pulmonary nodules: a single centre retrospective evaluation of the 2011 IASLC adenocarcinoma classification system. *Lung Cancer*. 2020;147:39-44.
27. Travis WD, Asamura H, Bankier AA, et al. The IASLC lung cancer staging project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11(8):1204-1223.
28. Li D, Deng C, Wang S, Li Y, Zhang Y, Chen H. Ten-year follow-up results of pure ground-glass opacity-featured lung adenocarcinomas after surgery. *Ann Thorac Surg*. 2023;116(2):230-237. https://doi.org/10.1016/j.athoracsur.2023.01.014
29. Koike H, Ashizawa K, Tsutsui S, et al. Surgically resected lung adenocarcinoma: do heterogeneous GGNs and part-solid nodules on thin-section CT show different prognosis? *Jpn J Radiol*. 2023;41(2):164-171.
30. Chang B, Hwang JH, Choi YH, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. *Chest*. 2013;143(1):172-178.
31. Lee HW, Jin KN, Lee JK, et al. Long-term follow-up of ground-glass nodules after 5 years of stability. *J Thorac Oncol*. 2019;14(8):1370-1377.
32. Bak SH, Lee HY, Kim JH, et al. Quantitative CT scanning analysis of pure ground-glass opacity nodules predicts further CT scanning change. *Chest*. 2016;149(1):180-191.
33. 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(11):1245-1250.
34. Dingemans AC, Reck M, Westeel V, eds. *Lung Cancer*. European Respiratory Society; 2015.
35. Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med*. 2015;162(7):485-491.
36. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol*. 2014;15(12):1332-1341.
37. Han D, Heuvelmans MA, Oudkerk M. Volume versus diameter assessment of small pulmonary nodules in CT lung cancer screening. *Transl Lung Cancer Res*. 2017;6(1):52-61.
38. Lee JH, Hwang EJ, Lim WH, Goo JM. Determination of the optimum definition of growth evaluation for indeterminate pulmonary nodules detected in lung cancer screening. *PLoS One*. 2022;17(9):e0274583.
39. Devaraj A, van Ginneken B, Nair A, Baldwin D. Use of volumetry for lung nodule management: theory and practice. *Radiology*. 2017;284(3):630-644.
40. Fischbach F, Knollmann F, Griesshaber V, Freund T, Akkol E, Felix R. Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness. *Eur Radiol*. 2003;13(10):2378-2383.
41. Godoy MCB, Kim TJ, White CS, et al. Benefit of computer-aided detection analysis for the detection of subsolid and solid lung nodules on thin- and thick-section CT. *AJR Am J Roentgenol*. 2013;200(1):74-83.
42. Liu JA, Yang IY, Tsai EB. Artificial intelligence (AI) for lung nodules, from the AJR special series on AI applications. *AJR Am J Roentgenol*. 2022;219(5):703-712.
43. Callister MEJ, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules: accredited by NICE. *Thorax*. 2015;70(suppl 2):ii1-ii54.
44. Henschke CI, Yip R, Smith JP, et al. CT Screening for lung cancer: part-solid nodules in baseline and annual repeat rounds. *AJR Am J Roentgenol*. 2016;207(6):1176-1184.
45. Lee SM, Park CM, Goo JM, et al. Transient part-solid nodules detected at screening thin-section CT for lung cancer: comparison with persistent part-solid nodules. *Radiology*. 2010;255(1):242-251.
46. Parekh M, Donuru A, Balasubramanya R, Kapur S. Review of the chest CT differential diagnosis of ground-glass opacities in the COVID era. *Radiology*. 2020;297(3):E289-E302.
47. Chu Z, Li W, Fu B, Lv F. CT characteristics for predicting invasiveness in pulmonary pure ground-glass nodules. *AJR Am J Roentgenol*. 2020;215(2):351-358.
48. 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(3):309-314.
49. Lee SW, Leem CS, Kim TJ, et al. The long-term course of ground-glass opacities detected on thin-section computed tomography. *Respir Med*. 2013;107(6):904-910.
50. Matsuguma H, Mori K, Nakahara R, et al. Characteristics of subsolid pulmonary nodules showing growth during follow-up with CT scanning. *Chest*. 2013;143(2):436-443.
51. Cho J, Kim ES, Kim SJ, et al. Long-term follow-up of small pulmonary ground-glass nodules stable for 3 years: implications of the proper follow-up period and risk factors for subsequent growth. *J Thorac Oncol*. 2016;11(9):1453-1459.
52. Yip R, Li K, Liu L, et al. Controversies on lung cancers manifesting as part-solid lung nodules. *Eur Radiol*. 2018;28(2):747-759.
53. Zhang C, Pan Y, Li H, et al. Extent of surgical resection for radiologically subsolid T1N0 invasive lung adenocarcinoma: when is a wedge resection acceptable? *J Thorac Cardiovasc Surg*. 2024;167(3):797-809.e2. https://doi.org/10.1016/j.jtcvs.2023.06.010
54. Fu F, Chen Z, Chen H. Treating lung cancer: defining surgical curative time window. *Cell Res*. 2023;33(9):649-650.
55. Liu LH, Liu M, Wei R, et al. CT findings of persistent pure ground glass opacity: can we predict the invasiveness? *Asian Pac J Cancer Prev*. 2015;16(5):1925-1928.
56. Xiang W, Xing Y, Jiang S, et al. Morphological factors differentiating between early lung adenocarcinomas appearing as pure ground-glass nodules measuring $\leq$10 mm on thin-section computed tomography. *Cancer Imag*. 2014;14(1):33.
57. Xing Y, Li Z, Jiang S, Xiang W, Sun X. Analysis of pre-invasive lung adenocarcinoma lesions on thin-section computerized tomography. *Clin Respir J*. 2015;9(3):289-296.
58. Yue X, Liu S, Liu S, et al. HRCT morphological characteristics distinguishing minimally invasive pulmonary adenocarcinoma from invasive pulmonary adenocarcinoma appearing as subsolid nodules with a diameter of $\leq$3 cm. *Clin Radiol*. 2018;73(4):411.e7.
59. Zhang Y, Shen Y, Qiang JW, Ye JD, Zhang J, Zhao RY. HRCT features distinguishing pre-invasive from invasive pulmonary adenocarcinomas appearing as ground-glass nodules. *Eur Radiol*. 2016;26(9):2921-2928.
60. Yip R, Wolf A, Tam K, et al. Outcomes of lung cancers manifesting as nonsolid nodules. *Lung Cancer*. 2016;97:35-42.
61. Hattori A, Hirayama S, Matsunaga T, et al. Distinct clinicopathologic characteristics and prognosis based on the presence of ground glass opacity component in clinical stage IA lung adenocarcinoma. *J Thorac Oncol*. 2019;14(2):265-275.
62. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. *J Thorac Oncol*. 2022;17(3):362-387.

63. Kim J, Chee CG, Cho J, Kim Y, Yoon MA. Diagnostic accuracy and complication rate of image-guided percutaneous transthoracic needle lung biopsy for subsolid pulmonary nodules: a systematic review and meta-analysis. *Br J Radiol*. 2021;94(1127):20210065.
64. Kiranantawat N, McDermott S, Petranovic M, et al. Determining malignancy in CT guided fine needle aspirate biopsy of subsolid lung nodules: is core biopsy necessary? *Eur J Radiol Open*. 2019;6:175-181.
65. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE study. *J Thorac Oncol*. 2019;14(3):445-458.
66. Styrvoky K, Schwalk A, Pham D, et al. Shape-sensing robotic-assisted bronchoscopy with concurrent use of radial endobronchial ultrasound and cone beam computed tomography in the evaluation of pulmonary lesions. *Lung*. 2022;200(6):755-761.
67. Wang N, Ma H, Huang H, Feng Y. Electromagnetic navigation bronchoscopy combined endobronchial ultrasound in the diagnosis of lung nodules. *Medicine (Baltimore)*. 2021;100(3):e23979.
68. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Non-Small Cell Lung Cancer. Version 1.2024. Accessed January 8, 2024. https://www.nccn.org/guidelines/guidelines-detail?category=I&id=1450
69. Zhuge L, Huang Y, Wang S, et al. Preoperative brain MRI for clinical stage IA lung cancer: is routine scanning rational? *J Cancer Res Clin Oncol*. 2019;145(2):503-509.
70. Li H, Ye T, Li N, et al. Is (99m) Tc bone scintigraphy necessary in the preoperative workup for patients with cT1N0 subsolid lung cancer? A prospective multicenter cohort study. *Thorac Cancer*. 2021;12(4):415-419.
71. Cho H, Lee HY, Kim J, et al. Pure ground glass nodular adenocarcinomas: are preoperative positron emission tomography/computed tomography and brain magnetic resonance imaging useful or necessary? *J Thorac Cardiovasc Surg*. 2015;150(3):514-520.
72. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non–small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg*. 1995;60(3):615-622; discussion 622-623.
73. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399(10335):1607-1617.
74. Altorki N, Wang X, Kozono D, et al. Lobar or sublobar resection for peripheral stage IA non–small-cell lung cancer. *N Engl J Med*. 2023;388(6):489-498.
75. Cho JH, Choi YS, Kim J, Kim HK, Zo JI, Shim YM. Long-term outcomes of wedge resection for pulmonary ground-glass opacity nodules. *Ann Thorac Surg*. 2015;99(1):218-222.
76. Yano M, Yoshida J, Koike T, et al. Survival of 1737 lobectomy-tolerable patients who underwent limited resection for cStage IA non–small-cell lung cancer. *Eur J Cardiothorac Surg*. 2015;47(1):135-142.
77. Sagawa M, Oizumi H, Suzuki H, et al. A prospective 5-year follow-up study after limited resection for lung cancer with ground-glass opacity. *Eur J Cardiothorac Surg*. 2018;53(4):849-856.
78. Suzuki K, Watanabe SI, Wakabayashi M, et al. A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer. *J Thorac Cardiovasc Surg*. 2022;163(1):289-301.e2.
79. Li D, Deng C, Wang S, Li Y, Zhang Y, Chen H. Ten-year follow-up of lung cancer patients with resected adenocarcinoma in situ or minimally invasive adenocarcinoma: wedge resection is curative. *J Thorac Cardiovasc Surg*. 2022;164(6):1614-1622.e1.
80. Yamaguchi H, Sato M, Yamamoto K, et al. Virtual-assisted lung mapping in sublobar resection of small pulmonary nodules, long-term results. *Eur J Cardiothorac Surg*. 2022;61(4):761-768.
81. Ye T, Deng L, Xiang J, et al. Predictors of pathologic tumor invasion and prognosis for ground glass opacity featured lung adenocarcinoma. *Ann Thorac Surg*. 2018;106(6):1682-1690.
82. Ha KJ, Yun JK, Lee GD, et al. Surgical outcomes of radiographically noninvasive lung adenocarcinoma according to surgical strategy: wedge resection, segmentectomy, and lobectomy. *Korean J Thorac Cardiovasc Surg*. 2018;51(6):376-383.
83. Nishio W, Yoshimura M, Maniwa Y, et al. Re-assessment of intentional extended segmentectomy for clinical T1aN0 non-small cell lung cancer. *Ann Thorac Surg*. 2016;102(5):1702-1710.
84. Nakao M, Yoshida J, Goto K, et al. Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. *J Thorac Oncol*. 2012;7(10):1563-1566.
85. Fu F, Zhang Y, Wen Z, et al. Distinct prognostic factors in patients with stage I non–small cell lung cancer with radiologic part-solid or solid lesions. *J Thorac Oncol*. 2019;14(12):2133-2142.
86. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Importance of ground glass opacity component in clinical stage IA radiologic invasive lung cancer. *Ann Thorac Surg*. 2017;104(1):313-320.
87. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Prognostic impact of a ground glass opacity component in the clinical T classification of non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2017;154(6):2102-2110.e1.
88. Tsutani Y, Miyata Y, Nakayama H, et al. Appropriate sublobar resection choice for ground glass opacity-dominant clinical stage IA lung adenocarcinoma: wedge resection or segmentectomy. *Chest*. 2014;145(1):66-71.
89. Volterrani L, Guerrini S, Zanfrini E, et al. HRCT predictors of GGO surgical resection: histopathological and molecular correlation in the era of lung sparing surgery. *Lung Cancer*. 2022;166:70-75.
90. Asamura H, Hishida T, Suzuki K, et al. Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201. *J Thorac Cardiovasc Surg*. 2013;146(1):24-30.
91. Im DJ, Lee SM, Han K, et al. Predictive factors of recurrence after resection of subsolid clinical stage IA lung adenocarcinoma. *Thorac Cancer*. 2021;12(6):941-948.
92. Nakama H, Yamada K, Saito H, et al. Sublobar resection for patients with peripheral small adenocarcinomas of the lung: surgical outcome is associated with features on computed tomographic imaging. *Ann Thorac Surg*. 2007;84(5):1675-1679.
93. Sim HJ, Choi SH, Chae EJ, et al. Surgical management of pulmonary adenocarcinoma presenting as a pure ground-glass nodule. *Eur J Cardiothorac Surg*. 2014;46(4):632-636; discussion 636.
94. Yoshida J, Nagai K, Yokose T, et al. Limited resection trial for pulmonary ground-glass opacity nodules: fifty-case experience. *J Thorac Cardiovasc Surg*. 2005;129(5):991-996.
95. Yoshida J, Ishii G, Hishida T, et al. Limited resection trial for pulmonary ground-glass opacity nodules: case selection based on high-resolution computed tomography-interim results. *Jpn J Clin Oncol*. 2015;45(7):677-681.
96. Zhang C, He Z, Cheng J, Cao J, Hu J. Surgical outcomes of lobectomy versus limited resection for clinical stage I ground-glass opacity lung adenocarcinoma 2 centimeters or smaller. *Clin Lung Cancer*. 2021;22(2):e160-e168.
97. Moon Y, Lee KY, Moon SW, Park JK. Sublobar resection margin width does not affect recurrence of clinical N0 non–small cell lung cancer presenting as GGO-predominant nodule of 3 cm or less. *World J Surg*. 2017;41(2):472-479.
98. Moon Y, Sung SW, Lee KY, Sim SB, Park JK. Pure ground-glass opacity on chest computed tomography: predictive factors for invasive adenocarcinoma. *J Thorac Dis*. 2016;8(7):1561-1570.
99. Bongiolatti S, Corzani R, Borgianni S, et al. Long-term results after surgical treatment of the dominant lung adenocarcinoma associated with ground-glass opacities. *J Thorac Dis*. 2018;10(8):4838-4848.
100. Shimada Y, Saji H, Otani K, et al. Survival of a surgical series of lung cancer patients with synchronous multiple ground-glass opacities, and the management of their residual lesions. *Lung Cancer*. 2015;88(2):174-180.
101. Kodama K, Higashiyama M, Okami J, et al. Oncologic outcomes of segmentectomy versus lobectomy for clinical T1a N0 M0 non–small cell lung cancer. *Ann Thorac Surg*. 2016;101(2):504-511.
102. Schneider BJ, Ismaila N, Aerts J, et al. Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. *J Clin Oncol*. 2020;38(7):753-766.
103. Colt HG, Murgu SD, Korst RJ, Slatore CG, Unger M, Quadrelli S. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2013;143(5):e437S-e454S.
104. Heuvelmans MA, Walter JE, Peters RB, et al. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: the NELSON study. *Lung Cancer*. 2017;113:45-50.
105. Lim HJ, Ahn S, Lee KS, et al. Persistent pure ground-glass opacity lung nodules $\geq$ 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. *Chest*. 2013;144(4):1291-1299.
106. Liu B, Ye X. Computed tomography-guided percutaneous microwave ablation: a novel perspective to treat multiple pulmonary ground-glass opacities. *Thorac Cancer*. 2020;11(9):2385-2388.
107. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines(R) insights: non–small cell lung cancer, version 2.2023. *J Natl Compr Cancer Netw*. 2023;21(4):340-350.

108. Gazdar AF, Minna JD. Multifocal lung cancers—clonality vs field cancerization and does it matter? *J Natl Cancer Inst*. 2009;101(8):541-543.
109. Kim HK, Choi YS, Kim J, Shim YM, Lee KS, Kim K. Management of multiple pure ground-glass opacity lesions in patients with bronchioloalveolar carcinoma. *J Thorac Oncol*. 2010;5(2):206-210.
110. Sato Y, Fujimoto D, Morimoto T, et al. Natural history and clinical characteristics of multiple pulmonary nodules with ground glass opacity. *Respirology*. 2017;22(8):1615-1621.
111. Detterbeck FC, Nicholson AG, Franklin WA, et al. The IASLC Lung Cancer Staging Project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol*. 2016;11(5):639-650.
112. Hattori A, Takamochi K, Oh S, Suzuki K. Prognostic classification of multiple primary lung cancers based on a ground-glass opacity component. *Ann Thorac Surg*. 2020;109(2):420-427.
113. Zhang Y, Li G, Li Y, et al. Imaging features suggestive of multiple primary lung adenocarcinomas. *Ann Surg Oncol*. 2020;27(6):2061-2070.
114. Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg*. 1975;70(4):606-612.
115. Liu M, He WX, Song N, Yang Y, Zhang P, Jiang GN. Discrepancy of epidermal growth factor receptor mutation in lung adenocarcinoma presenting as multiple ground-glass opacities. *Eur J Cardio Thorac Surg*. 2016;50(5):909-913.
116. Tian H, Bai G, Yang Z, et al. Multiple primary lung cancer: updates of clinical management and genomic features. *Front Oncol*. 2023;13:1034752.
117. Zheng R, Shen Q, Mardekian S, Solomides C, Wang ZX, Evans NR III. Molecular profiling of key driver genes improves staging accuracy in multifocal non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2020;160(2):e71-e79.
118. Patel SB, Kadi W, Walts AE, et al. Next-generation sequencing: a novel approach to distinguish multifocal primary lung adenocarcinomas from intrapulmonary metastases. *J Mol Diagn*. 2017;19(6):870-880.
119. Liu C, Liu C, Zou X, Shao L, Sun Y, Guo Y. Next-generation sequencing facilitates differentiating between multiple primary lung cancer and intrapulmonary metastasis: a case series. *Diagn Pathol*. 2021;16(1):21.
120. Li Y, Li X, Li H, et al. Genomic characterisation of pulmonary subsolid nodules: mutational landscape and radiological features. *Eur Respir J*. 2020;55(2):1901409.
121. Gao RW, Berry MF, Kunder CA, et al. Survival and risk factors for progression after resection of the dominant tumor in multifocal, lepidic-type pulmonary adenocarcinoma. *J Thorac Cardiovasc Surg*. 2017;154(6):2092-2099.e2.
122. Watanabe T, Tanahashi M, Suzuki E, et al. Surgical treatment for synchronous multiple primary lung cancer: is it possible to achieve both curability and preservation of the pulmonary function? *Thorac Cancer*. 2021;12(22):2996-3004.
123. Eriguchi T, Takeda A, Sanuki N, et al. Stereotactic body radiotherapy for operable early-stage non-small cell lung cancer. *Lung Cancer*. 2017;109:62-67.
124. Tomita N, Okuda K, Osaga S, Miyakawa A, Nakanishi R, Shibamoto Y. Surgery versus stereotactic body radiotherapy for clinical stage I non–small-cell lung cancer: propensity score-matching analysis including the ratio of ground glass nodules. *Clin Transl Oncol*. 2021;23(3):638-647.
125. Ye X, Fan W, Wang H, et al. Expert consensus workshop report: guidelines for thermal ablation of primary and metastatic lung tumors (2018 edition). *J Cancer Res Ther*. 2018;14(4):730-744.
126. Uhlig J, Ludwig JM, Goldberg SB, Chiang A, Blasberg JD, Kim HS. Survival rates after thermal ablation versus stereotactic radiation therapy for stage 1 non–small cell lung cancer: a National Cancer Database Study. *Radiology*. 2018;289(3):862-870.
127. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv1-iv21.
128. Han X, Yang X, Huang G, et al. Safety and clinical outcomes of computed tomography-guided percutaneous microwave ablation in patients aged 80 years and older with early-stage non–small cell lung cancer: a multicenter retrospective study. *Thorac Cancer*. 2019;10(12):2236-2242.
129. Kodama H, Yamakado K, Hasegawa T, et al. Radiofrequency ablation for ground-glass opacity-dominant lung adenocarcinoma. *J Vasc Interv Radiol*. 2014;25(3):333-339.
130. Yang X, Ye X, Lin Z, et al. Computed tomography-guided percutaneous microwave ablation for treatment of peripheral ground-glass opacity-lung adenocarcinoma: a pilot study. *J Cancer Res Ther*. 2018;14(4):764-771.
131. Liu S, Zhu X, Qin Z, et al. Computed tomography-guided percutaneous cryoablation for lung ground-glass opacity: a pilot study. *J Cancer Res Ther*. 2019;15(2):370-374.
132. Huang G, Yang X, Li W, et al. A feasibility and safety study of computed tomography-guided percutaneous microwave ablation: a novel therapy for multiple synchronous ground-glass opacities of the lung. *Int J Hyperthermia*. 2020;37(1):414-422.
133. Liu B, Zhang Y, Su L, Wang R. Treatment options for pulmonary multifocal ground glass opacity type adenocarcinoma: Surgery combine thermal ablation? *J Interv Med*. 2020;3(4):180-183.
134. Yotsukura M, Asamura H, Motoi N, et al. Long-term prognosis of patients with resected adenocarcinoma in situ and minimally invasive adenocarcinoma of the lung. *J Thorac Oncol*. 2021;16(8):1312-1320.
135. ClinicalTrials. gov. Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy (VALOR). Accessed January 8, 2024. https://clinicaltrials.gov/study/NCT02984761
136. Li C, Ni Y, Liu C, et al. Mediastinal lymph node dissection versus spared mediastinal lymph node dissection in stage IA non–small cell lung cancer presented as ground-glass nodules: study protocol of a phase III, randomized, multi-centre trial in China. *BMJ Open*. 2023;13(10):e075242.
137. Zhang Y, Deng C, Zheng Q, et al. Selective mediastinal lymph node dissection strategy for clinical T1N0 invasive lung cancer: a prospective, multi-center, clinical trial. *J Thorac Oncol*. 2023;18(7):931-939.
138. Petranovic M, Raoof S, Digumarthy SR, et al. Liquid biopsy, diagnostic imaging, and future syndergies. *J Am Coll Radiol*. 2022;19(2 Pt B):336-343.
139. Scafoglio C, Villegas B, Abdelhady G, et al. Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. *Sci Transl Med*. 2018;10(467):eaat5933.
140. de Margerie-Mellon C, Onken A, Heidinger BH, Vanderlaan PA, Bankier AA. CT manifestations of tumor spread through airspaces in pulmonary adenocarcinomas presenting as subsolid nodules. *J Thorac Imaging*. 2018;33(6):402-408.

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

Writing group member	Primary affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or nonfinancial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Carol C. Wu, MD	MD Anderson Cancer Center	Houston, Tex		X										Royalties from Elsevier, Inc, for book chapters
Kenji Suzuki, MD	Juntendo University Hospital	Tokyo, Japan												Nothing to disclose
Dennis A Wigle, MD PhD	Mayo Clinic	Rochester Minn	x						X		x	x		Biostage, Evelo
Momen M. Wahidi, MD, MBA	Northwestern University Feinberg School of Medicine	Chicago, Ill			x									Olympus, Pulmonx, Cook, Veracyte (payments made to me)
Joseph B. Shrager, MD	Stanford University School of Medicine, Department of Cardiothoracic Surgery, Division of Thoracic Surgery	Stanford, Calif	x		x		x			x	x			Varian Inc, grant funding; payment to institution Becton Dickinson, consulting; payment to individual Lungpacer, Inc., grant funding and clinical advisory board; payment to both institution and individual Society of Thoracic Surgeons, Chair of Workforce on General Thoracic Surgery
Claudia I. Henschke, MD	Icahn School of Medicine at Mount Sinai	New York, NY												Dr Claudia Henschke is a named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on computed tomography scans of the chest that are owned by Cornell Research Foundation (CRF). Since 2009, Dr Henschke does not accept any financial benefit from these patents including royalties and any other proceeds related to the patents or patent applications owned by CRF. Dr Henschke is the President and serve on the board of the Early Diagnosis and Treatment Research Foundation. She receives no compensation from the Foundation. The Foundation is established to provide grants for projects, conferences, and public databases for research on early diagnosis and treatment of diseases. Recipients include I-ELCAP, among others. The funding comes from a variety of sources including philanthropic donations, grants and contracts with agencies (federal and nonfederal), imaging and pharmaceutical companies relating to image processing assessments. The various sources of funding exclude any funding from tobacco companies or tobacco-related sources. Dr Claudia

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APPENDIX E1. Continued

Writing group member	Primary affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or nonfinancial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
														Henschke is on the advisory board of LungLife AI without compensation.
Tina D. Tailor	Duke Health	Durham, NC												Nothing to disclose
Anthony W. Kim	Division of Thoracic Surgery, Keck School of Medicine, University of Southern California	Los Angeles, Calif			x									Medtronic - Advisory Board (unrelated to anything having to do with this manuscript) Roche Genentech - Steering Committee (unrelated to anything having to do with this article)
Michael Hsin	Queen Mary Hospital	Hong Kong China SAR												Nothing to disclose
Ashley Elizabeth Prosper, MD	Dept. of Radiological Sciences, University of California at Los Angeles	Los Angeles, Calif	x											Research grants & clinical trials current awards grant/ trial number: investigator initiated research | unrestricted gift | $2,668,578 total source: Wyeth foundation date: 1/2021-March 31, 2025: Title: utilizing spheres of influence to increase lung screening. PIs: Prosper A, Milch H, Hsu W, Fischer C. Description: this project aims to improve utilization of lung screening by pairing it with breast screening in female patients who are eligible for both screening exams. In addition, we assess whether women who engage in screening can influence eligible members of their community to adhere to lung screening recommendations. Grant/trial number: nct04165564. Aency: American College of Radiology | Boston University | $196,275 total date: June 02, 2020-March 31, 2023 (currently undergoing renewal through December 31, 2024). Title: decamp 1-plus. PIs: Aberle D, Washko G, Duan F, Kadara H, Fujimoto J, Billatos E. Role: UCLA site PI. Description: to develop and validate molecular biomarkers that can serve as tools for the early detection of lung cancer grant/trial number: 20202230. Agency: American College of Radiology | $100,000 total date: September 01, 2020-August 31, 2021, 2 y no cost extension through August 31, 2023/ Title: Lung cancer screening in African Americans, a community engagement project PIs: prosper a description: to develop lung cancer screening education and outreach tools specifically for the African American community. Grant/trial number: IRB

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APPENDIX E1. Continued

Writing group member	Primary affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or nonfinancial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
														#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. PIs: 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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APPENDIX E1. Continued

Writing group member	Primary affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or nonfinancial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
														correlation via outlier analysis. Grant/trial number: r01ca210360. agency: NIH/National Cancer Institute | $1,646,404 total date: September 202016-August 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: Medqia FibroGen 093. Description: a phase 3, randomized, double-blind, trial of pamrevlumab (fg-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)
Jane Yanagawa, MD	UCLA David Geffen School of Medicine	Los Angeles, Calif	x			X		x		x		x		Lungevity Foundation Grant NCCN (honoraria) IDEOlogy (honoraria and travel for speaking commitment) DSMB committee chair NIH National Institute of Neurological Disorders and Stroke UH3 NS119772 ICONA co-founder (stock)
Kazuhiro Yasufuku MD, PhD	Toronto General Hospital, University Health Network	Toronto, Ontario, Canada	x		x					x			x	Industry-sponsored research grants: Olympus Corporation, Johnson & Johnson, ODS Medical Inc. Consultant: Olympus America Inc, Johnson & Johnson, Medtronic Research Collaboration: OKF Technology Advisory Board: Olympus America Inc, Johnson & Johnson, Medtronic

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APPENDIX E1. Continued

Writing group member	Primary affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or nonfinancial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
James Huang, MD	Memorial Sloan Kettering Cancer Center	New York, NY												Nothing to disclose
David R. Jones	Memorial Sloan Kettering Cancer Center	New York, NY				X				x	x			AstraZeneca - honoraria, Advisory Board. Merck - Clinical Trial Steering Committee. Genentech – honoraria. American Association for Thoracic Surgery - Board of Directors.
Haiquan Chen, PhD, MD	Fudan University Shanghai Cancer Center	Shanghai, China												Nothing to disclose

Witting Group member	Primary Affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Carol C. Wu, MD	MD Anderson Cancer Center	Houston, TX		x										Royalties from Elsevier, Inc for book chapters
Kenji Suzuki, MD	Juntendo University Hospital	Tokyo, Japan												Nothing to disclose
Dennis A Wigle, MD PhD	Mayo Clinic	Rochester MN USA	x						x		x	x		Biostage, Evelo
Momen M. Wahidi, MD, MBA	Northwestern University Feinberg School of Medicine	Chicago, IL			x									Olympus, Pulmonx, Cook, Veracyte (payments made to me)
Joseph B. Shrager, MD	Stanford University School of Medicine, Department of Cardiothoracic Surgery, Division of Thoracic Surgery	Stanford, CA, USA	x		x		x			x	x			Varian Inc, grant funding; payment to institution Becton Dickinson, consulting; payment to individual Lungpacer, Inc., grant funding and clinical advisory board; payment to both institution and individual Society of Thoracic Surgeons, Chair of Workforce on General Thoracic Surgery

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APPENDIX E1. Continued

Witting Group member	Primary Affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Claudia I. Henschke, MD	Icahn School of Medicine at Mount Sinai	New York, NY, USA							x					Dr Claudia Henschke is a named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on CT scans of the chest which are owned by Cornell Research Foundation (CRF). Since 2009, Dr Henschke does not accept any financial benefit from these patents including royalties and any other proceeds related to the patents or patent applications owned by CRF. Dr Henschke is the President and serve on the board of the Early Diagnosis and Treatment Research Foundation. She receives no compensation from the Foundation. The Foundation is established to provide grants for projects, conferences, and public databases for research on early diagnosis and treatment of diseases. Recipients include I-ELCAP, among others. The funding comes from a variety of sources including philanthropic donations, grants and contracts with agencies (federal and non-federal), imaging and pharmaceutical companies relating to image processing assessments. The various sources of funding exclude any funding from tobacco companies or tobacco-related sources. Dr Claudia Henschke is on the advisory board of LungLife AI without compensation.
fAugust Tina D. Tailor	Duke Health	Durham, NC, USA												Nothing to disclose
Anthony W. Kim	Division of Thoracic Surgery, Keck School of Medicine, University of Southern California	Los Angeles, CA			x									Medtronic - Advisory Board (unrelated to anything having to do with this manuscript) Roche Genentech - Steering Committee (unrelated to anything having to do with this manuscript)
Michael Hsin	Queen Mary Hospital	Hong Kong China SAR												Nothing to disclose

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APPENDIX E1. Continued

Witting Group member	Primary Affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Ashley Elizabeth Prosper, MD	Dept. of Radiological Sciences, University of California at Los Angeles	Los Angeles, CA	x											RESEARCH GRANTS & CLINICAL TRIALS Current Awards Grant/trial number: Investigator Initiated Research | Unrestricted gift | $2,668,578 total Source: Wyeth Foundation Date: April 1, 2021-March 31, 2025 Title: Utilizing Spheres of Influence to Increase Lung Screening PIs: Prosper A, Milch H, Hsu W, Fischer C Description: This project aims to improve utilization of lung screening by pairing it with breast screening in female patients who are eligible for both screening exams. In addition, we assess whether women who engage in screening can influence eligible members of their community to adhere to lung screening recommendations. Grant/trial number: NCT04165564 Agency: American College of Radiology | Boston University | $196,275 total Date: June 02, 2020-March 31, 2023 (currently undergoing renewal through December 31, 2024). Title: DECAMP 1-PLUS PIs: Aberle D, Washko G, Duan F, Kadara H, Fujimoto J, Billatos E Role: UCLA Site PI Description: To develop and validate molecular biomarkers that can serve as tools for the early detection of lung cancer Grant/trial number: 20202230 Agency: American College of Radiology | $100,000 total Date: September 01, 2020-August 31, 2021, 2 y no cost extension through August 31, 2021 Title: Lung Cancer Screening in African Americans, a Community Engagement Project PIs: Prosper A Description: To develop Lung Cancer Screening education and outreach tools specifically for the African American Community. Grant/trial number: IRB #19-000133 Agency: Edwards Lifesciences | $11,673 total (to date) Date: June 17, 2019-July 8, 2023 Title: Multicenter Trial of Congenital

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Witting Group member	Primary Affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
														Pulmonic Valve Dysfunction Studying the SAPIEN 3 Interventional THV with the Alterra Adaptive Present. 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: NIH/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/NHBIB | $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 PIs: Ennis D Role: Co-Investigator Description: To define the precision and reproducibility of several diagnostic cardiac MRI

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APPENDIX E1. Continued

Witting Group member	Primary Affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
														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: Medqia Fibrogen 093 Description: A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-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)

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Witting Group member	Primary Affiliation	Location	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/or travel	Patents planned, issued or pending	Participation on a Data Safety Monitoring Board or Advisory Board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Jane Yanagawa, MD	UCLA David Geffen School of Medicine	Los Angeles	x			x		x		x		x		Lungevity Foundation Grant NCCN (honoraria) IDEOlogy (honoraria and travel for speaking commitment) DSMB committee chair NIH NINDS UH3 NS119772 ICONA co-founder (stock)
Kazuhiro Yasufuku MD, PhD	Toronto General Hospital, University Health Network	Toronto, ON, Canada	x		x					x			x	Industry sponsored research grants: Olympus Corporation, Johnson & Johnson, ODS Medical Inc Consultant: Olympus America Inc, Johnson & Johnson, Medtronic Research Collaboration: OKF Technology Advisory Board: Olympus America Inc, Johnson & Johnson, Medtronic
James Huang, MD	Memorial Sloan Kettering Cancer Center	New York, NY, USA												Nothing to disclose
David R. Jones	Memorial Sloan Kettering Cancer Center	New York, NY				x				x	x			AstraZeneca - Honoraria, Advisory Board Merck - Clinical Trial Steering Committee Genentech - Honoraria AATS - Board of Directors
Haiquan Chen, PhD, MD	Fudan University Shanghai Cancer Center	Shanghai, China												Nothing to disclose

Reviewer relationships with industry and other entities

Reviewer	Primary affiliation	Location	Grants or contracts	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Support for attending meetings and/or travel	Participation on a Data Safety Monitoring Board or Advisory Board	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Anil Vachani, MD, MSCE	Associate Professor of Medicine at the Hospital of the University of Pennsylvania and the Veteran's Administration Medical Center	Philadelphia, Pa	x	x			x	Precyte, Inc, Optellum, Ltd, NCCN, MagArray, Gordon and Betty Moore Foundation, Lungevity Foundation, Delfi Diagnostics, Johnson and Johnson (direct payment), Intuitive Surgical (direct payment), DELFI Diagnostics (unpaid)

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APPENDIX E1. Continued

			Reviewer relationships with industry and other entities					
Reviewer	Primary affiliation	Location	Grants or contracts	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Support for attending meetings and/or travel	Participation on a Data Safety Monitoring Board or Advisory Board	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Hari B. Keshava, MD, MS, FACS	University of California, Irvine	Orange, Calif		x	x	x		Aztrazeneca, Merck, Noah Medical, Intuitive Surgical
Milena Petranovic, MD	Massachusetts General Hospital	Boston, Mass	x					IBM, Novartis (not related to topic of current manuscript)
René Horsleben Petersen, MD PhD	Department of Cardiothoracic Surgery, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark	Copenhagen, Denmark	x		x		x	Speaker fee Medtronic, AstraZeneca, Medela and AMBU. Advisory Board: AstraZeneca, BMS, Roche, MSD. Research Grants: Novo Nordisk Foundation, X-vivo, Medtronic.
Hong Kwan Kim, MD	Samsung Medical Center	Seoul, South Korea						Nothing to disclose
Mark F. Berry, MD	Stanford University	Stanford, Calif						Nothing to disclose
Erin A GillasPIe, MD, MPH, FACS	Creighton University Medical Center	Omaha, Neb		x	x	x		Astra Zeneca, Intuitive Surgical, Ideology Health, ASCO, BMS, Genentech, Daiichi Sankyo