Review Article

A narrative review of the clinical approach to subsolid pulmonary nodules

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Background and Objective: The widespread use of chest computed tomography (CT) for lung cancer screening has led to increased detection of subsolid pulmonary nodules. The management of subsolid nodules (SSNs) is challenging since they are likely to grow slowly and a long-term follow-up is needed. In this review, we discuss the characteristics, natural history, genetic features, surveillance, and management of SSNs.

Methods: PubMed and Google Scholar were searched to identify relevant articles published in English between January 1998 and December 2022 using the following keywords: "subsolid nodule", "ground-glass nodule (GGN)", and "part-solid nodule (PSN)".

Key Content and Findings: The differential diagnosis of SSNs includes transient inflammatory lesions, focal fibrosis, and premalignant or malignant lesions. Long-term CT surveillance follow-up is needed to manage SSNs that persist for >3 months. Although most SSNs have an indolent clinical course, PSNs may have a more aggressive clinical course than pure GGNs. The proportion of growth and the time to grow is higher and shorter in PSN than pure GGN. In lung adenocarcinoma manifesting as SSNs, *EGFR* mutations were the major driver mutations. Guidelines are available for the management of incidentally detected and screening-detected SSNs. The size, solidity, location, and number of SSNs are important factors in determining the need for surveillance and surgical resection, as well as the interval of follow-up. Positron emission tomography/CT and brain magnetic resonance imaging (MRI) are not recommended for the diagnosis of SSNs, especially for pure GGNs. Periodic CT surveillance and lung-sparing surgery are the main strategies for the management of persistent SSNs. Nonsurgical treatment options for persistent SSNs include stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA). For multifocal SSNs, the timing of repeated CT scans and the need for surgical treatment are decided based on the most dominant SSN(s).

Conclusions: The SSN is a heterogeneous disease and a personalized medicine approach is required in the future. Future studies of SSNs should focus on their natural history, optimal follow-up duration, genetic features, and surgical and nonsurgical treatments to improve the corresponding clinical management. All these efforts will lead to the personalized medicine approach for the SSNs.

Keywords: Subsolid nodule (SSN); pure ground-glass nodule; part-solid nodule (PSN); ground-glass opacity (GGO); lung adenocarcinoma

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Introduction

Lung cancer is the leading cause of cancer-related mortality, and its incidence is increasing worldwide (1,2). The National Lung Screening Trial demonstrated the utility of low-dose helical computed tomography (LDCT) for the early detection of lung cancer and improvement of lung cancer-specific mortality (3,4). Chest LDCT is becoming widely used for lung cancer screening in high-risk groups (3,5) and in some low-risk groups (e.g., never-smokers and women) (6,7). The widespread use of LDCT has increased the detection of pulmonary nodules, including subsolid nodules (SSNs). SSNs comprise a large proportion of pulmonary nodules and are characterized by ground-glass opacity (GGO), which exhibits higher attenuation than normal lung tissue without the obliteration of vascular and bronchial margins (8). SSNs are classified as part-solid nodules (PSNs) or mixed ground-glass nodules (GGNs) and nonsolid nodules or pure GGNs (8). SSNs may be transient or persistent; compared with transient SSNs, persistent SSNs are more likely to be premalignant or malignant (9). Although SSNs usually have indolent progression (10), their management is complicated by variable growth rates (11) and the need for long-term follow-up with repeated CT scans.

This review discusses the characteristics, natural history, and genetic features of SSNs. It also addresses the surveillance and management of SSNs. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5246/rc).

Methods

PubMed and Google Scholar were searched to identify relevant articles published in English using the following keywords: "subsolid nodule", "ground-glass nodule (GGN)", and "part-solid nodule (PSN)" (*Table 1*).

Differential diagnosis and pathology

Multiple differential diagnoses should be considered before SSN is diagnosed, including transient lesions such as inflammation, focal pneumonia, hemorrhage, or pulmonary infiltration with eosinophilia (12). The differential diagnoses of SSNs that persist for >3 months include focal fibrosis and premalignant or malignant lesions, such as atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IA) (13,14).

Transient or benign lesions

Among newly detected SSNs, 40–63% resolved during follow-up (10,15-17). In the NELSON study cohort, 63% of SSNs had resolved by the 1-, 3-, and 5.5-year follow-up screening (15). Therefore, the persistence of newly detected SSNs should be ascertained before biopsy or surgical resection.

Pulmonary infiltration with eosinophilia is characterized by asymptomatic migrating pulmonary infiltrates, with an increased number of peripheral blood eosinophils and spontaneous resolution (18) (*Figure 1*). This condition is the result of parasitic infections or drug use. Toxocariasis is a helminthozoonosis caused by *Toxocara canis* or *Toxocara catis*. Humans are infected through the ingestion of embryonated eggs or consumption of raw meat from paratenic hosts, such as chickens, lambs, rabbits, or cows (19). *Toxocara*-induced visceral larva migrans may cause pulmonary infiltrates. Raw meat and uncooked cow liver are popular dishes in South Korea. In a previous study, we found that blood eosinophilia and Toxocara seropositivity were associated with transient and migratory pulmonary infiltrates, including SSNs, on chest CT (20). Therefore, pulmonary toxocariasis is an important differential diagnosis of new pulmonary infiltrates, including SSNs, in patients with a history of raw meat intake.

Premalignant or malignant lesions

The 2011 classification of lung adenocarcinoma introduced the concepts of AIS and MIA while omitting terms such as bronchioloalveolar carcinoma and mixed subtype adenocarcinoma (21). AAH is characterized by small (≤5 mm) localized foci of proliferating mild-to-moderate atypical type II pneumocytes and/or club cells that line the alveolar walls and respiratory bronchioles (21). AIS has a predominantly lepidic pattern of ≤3 cm neoplastic cell growth along the alveolar walls without stromal, vascular, or pleural invasion. MIA is characterized by a small solitary adenocarcinoma with ≤5 mm of invasion and ≤3 cm overall size in a lepidic background (21). IA is characterized by >5 mm invasion and classified as lepidic, acinar, papillary, micropapillary, or solid predominant (21,22).

There are no reliable correlations between histopathological findings and radiological appearance. Approximately 25–50% of resected pure GGNs have invasive components (23-27). Ichinose *et al.* (25) reported that MIA and IA comprised 31% and 4% of 180 resected pure GGNs, respectively. Additionally, a higher maximum CT

Table 1 Summary of search strategy

Items	Specification
Search date	The initial search was conducted on April 1, 2022
Databases and other sources searched	PubMed and Google Scholar
Search terms	Subsolid nodule, ground-glass nodule, and part-solid nodule
Timeframe	English abstracts and articles published before December 2022
Inclusion criteria	English abstracts and articles
Selection process	Two pulmonologists (BGK and SWU) independently conducted the selection. Consensus was reached via discussion after selection

attenuation value (≥–300 Hounsfield units) was a useful predictor of histological invasiveness.

Natural history of SSNs

An understanding of the natural history of SSNs may improve their management. However, it has not been fully elucidated because they were first described <30 years ago (i.e., in the mid-1990s) (28,29). In this section, we summarize the results of studies concerning the long-term course of SSNs.

Natural courses of pure GGNs and PSNs

Table 2 presents recent studies concerning the natural history of SSNs (10,15,26,30-39). The type (pure GGNs or PSNs) and size of included nodules, as well as the follow-up duration, varied among studies. Nodule growth was most commonly defined as an increase in diameter of ≥2 mm and/or the development of a new solid portion (*Table 2*). However, one study defined nodule growth as a volume increase of ≥25% (15). The existing literature suggests that pure GGNs have an indolent natural course, whereas PSNs have a less indolent course.

In a previous study, we explored the natural history of 122 pure GGNs for a median follow-up interval of 59 months; we found per-person and per-nodule growth rates of 13.5% (12/89) and 9.8% (12/122), respectively (10). The volume doubling time (VDT) is defined as the time required for a growing nodule to double its volume (40). In this study, we calculated VDT according to a modified method of the Schwartz formula (41). The median volume VDT of the 12 growing SSNs was 769 days (range, 330–3,031 days). Therefore, almost 90% of pure GGNs did not grow during a median follow-up interval of 5 years, and the growing pure GGNs had slow growth rates (VDT >330 days) (10). Matsuguma *et al.* (31) investigated the natural courses of 98 pure GGNs (nonsolid nodule) and 76 PSNs. The respective 2- and 5-year cumulative growth rates were 13% and 23% in patients with pure GGNs, whereas they were 38% and 55% in patients with PSNs (31). In 2016, a Japanese group performed a prospective multicenter study to record the natural history of 1,229 SSNs (accrual period: 2009–2011; mean follow-up duration: 4.3 years) (33). The 2- and 5-year probabilities of growth were 2% and 14%, 12% and 24%, and 17% and 48% for pure GGNs, heterogeneous GGNs, and PSNs, respectively. Sawada *et al.* (36) found that all patients with a consolidation tumor ratio (C/T ratio) >0 exhibited tumor growth within 3 years; however, in 16% of patients with a C/T ratio of 0 (pure GGN), >3 years of follow-up was necessary to identify tumor growth. C/T ratio was defined as the proportion of the maximum consolidation diameter divided by the maximum tumor diameter (36). Cho *et al.* (32) found that, among SSNs that had remained stable during the initial 3 years, the rate of subsequent growth was 3.3%. Therefore, the proportion of growth and the time to growth are higher and shorter, respectively, in PSNs than in pure GGNs.

Natural course of SSNs after stability for 5 years

In 2 recent studies analyzing nodules that remained stable for 5 years after detection, some SSNs demonstrated growth after >5 years of follow-up (37,38). In 2019, Lee *et al.* (37) analyzed 208 SSNs with a median follow-up interval of 136 months. They reported that 13.0% of SSNs grew during follow-up after remaining stable for the initial 5 years. Approximately 70% of growing nodules had a size ≤6 mm at the time of detection. In 2020, another study

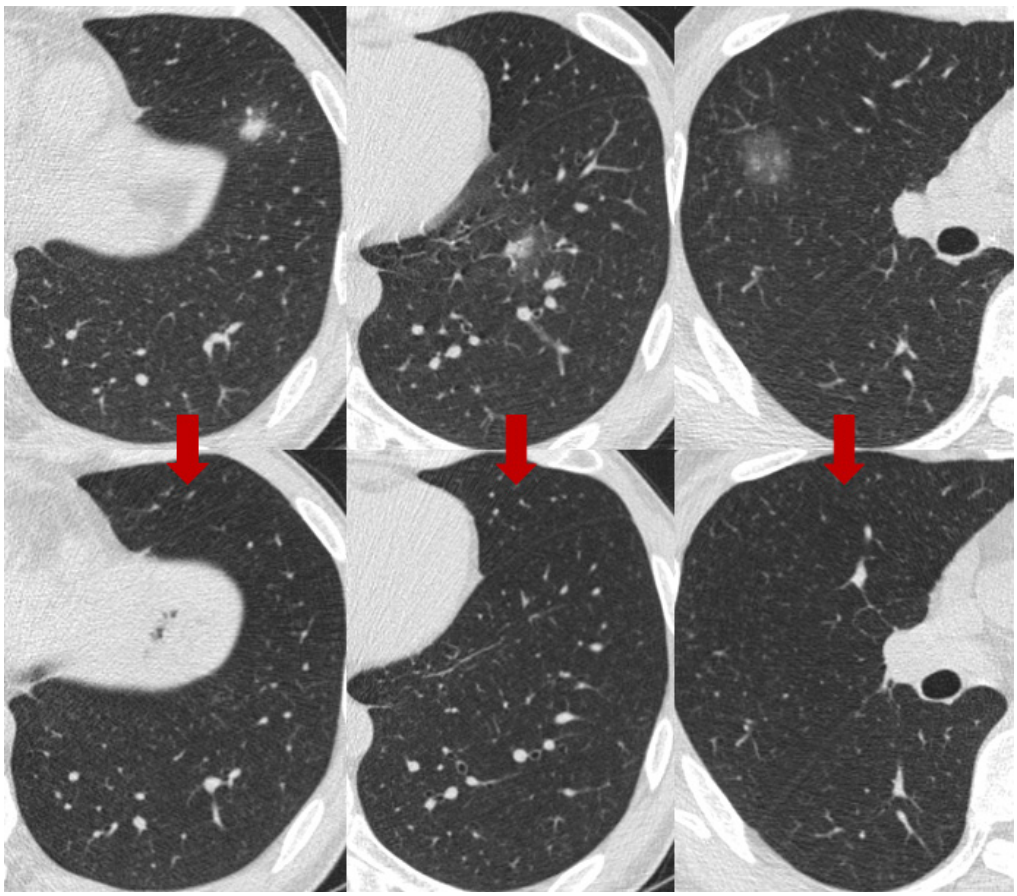

Figure 1 Pulmonary infiltration with eosinophilia. A 47-year-old man with a history of raw cow liver intake had a peripheral blood eosinophil proportion of 9.7% at the initial visit. The patient had positive findings in a Toxocara canis enzyme-linked immunosorbent assay. At the 3-month follow-up visit, the patient's multiple SSN lesions had improved without any treatment. The red arrows indicate the change from initial finding to follow-up. SSN, subsolid nodule.

evaluated 235 SSNs with a size ≥6 mm that had remained stable for 5 years (38); in that study, 5 (2.1%) nodules grew during a median follow-up interval of 112 months. Three of the five growing SSNs showed a change in clinical stage during follow-up: one from Tis to T1mi and two from T1mi to T1a. The results of these two studies support a longer follow-up duration (i.e., >5 years) for SSNs than the duration suggested by current guidelines. Further studies are needed to determine the optimal follow-up duration for SSNs.

Risk factors for SSN growth

Multiple studies have identified risk factors for SSN growth, including a large size (>10 mm) at the time of detection (10,26,31-35,42), history of lung cancer (31,32,34,35), smoking (43), the presence of a solid component (10,26,32,34,35,37), the presence of bubble lucency or air-bronchogram (32,37), male sex (26), the presence of EGFR mutation (11), and age ≥65 years (32,44). Although SSNs generally exhibit continuous slow growth, SSN size may paradoxically decrease when a solid component appears. Kaneda *et al.* (45) found that 47% of resected SSNs with adenocarcinoma showed a decrease in size during progression; the decrease in size usually coincided with the appearance of a solid component. Therefore, a mild decrease in SSN size suggests progression to IA and the need for careful follow-up.

Natural course of newly detected SSNs

Multiple recent studies have evaluated the course of SSNs

Table 2 Recent studies concerning the natural courses of pulmonary SSNs

Study	No. of patients/ SSNs	Inclusion criteria	Enrollment duration	Follow-up duration	Definition of growth	SSNs with growth	Volume doubling time	No. of nodules with pathological confirmation	Factors related to SSN growth
Chang, 2013 (10)	89/122	Pure GGNs	1997–2006	Median: 59 [25–140] months	Increase in size ≥2 mm on initial screening	12/122 (9.8%)	769 [330–3,031] days	11 nodules: 2 AIS; 6 MIA; 3 invasive ADC	Initial size; new development of internal solid portion
Kobayashi, 2013 (30)	61/108	(I) Lesion diameter ≤3 cm; (II) GGO proportion ≥50%; (III) observation without treatment in previous 6 months	1999–2012	Median: 4.2 years	Increase in size ≥2 mm	29/108 (27%)	–	26 nodules: 1 AAH; 1 AAH/AIS; 10 AIS; 1 AIS/MIA; 8 MIA; 5 invasive ADC	–
Lee, 2013 (26)	114/175; 143: pure GGNs; 32: PSNs	(I) Pure GGNs + PSNs (mixed GGNs); (II) persistent for >2 years without resection	2004–2011	Median: 45 [24–99] months	Increase in size ≥2 mm	46/175 (19.6%); 28: pure GGNs; 18: PSNs	Pure GGNs: 872±649 days; PSNs: 1,005±732 days	29 nodules: 2 interstitial fibrosis; 1AAH; 3 AIS; 11 MIA; 11 invasive ADC; 1 pleomorphic carcinoma	PSN; initial size (≥10 mm); single lesion (*vs.* multiple lesions)
Matsuguma, 2013 (31)	171/174	(I) Pure GGNs + PSNs; (II) diameter ≤2.0 cm; (III) GGO proportion >20%	2000–2008	Mean: 29 [1–136] months	(I) Increase in size ≥2 mm; (II) ≥2 mm of solid area emerged in a nonsolid nodule or growth of solid area by ≥2 mm	41/174 (23.6%)	–	56 nodules: 3 AAH; 36AIS; 11: MIA; 6 invasive ADC	Pure GGNs: lung cancer history and nodule diameter ≥10 mm. PSNs: none
Scholten, 2015 (15)	108/117	SSNs ≥5 mm	NELSON study	Median: 95 [20–110] months	(I) Increase in total volume or volume of solid component >25%; (II) increase in nodule mass ≥30%	Unresected nodules 13/84 (15.5%)	<400 days	33 nodules: 5 benign; 9 AIS; 19 invasive ADC	–
Cho, 2016 (32)	218/453; 438: pure GGNs; 15: PSNs	(I) Pure GGNs + PSNs; (II) nodules persistent and stable for 3 years	2003–2015	Median: 77.5 [38.1–117.1] months	(I) ≥2 mm increase in GGN size; (II) ≥2 mm increase in solid component of PSN; (III) emerging new solid component of any size in pure GGN	15/453 (3.3%)	1,199 [575–10,486] days	7 nodules: 2 MIA; 5 invasive ADC	Age ≥65 years, lung cancer history, initial size ≥8 mm, presence of solid component, air bronchogram
Kakinuma, 2016 (33)	795/1,229; 1,046: pure GGNs; 81: heterogeneous[†] GGNs; 102: PSNs	(I) Pure GGNs ≤30 mm; (II) SSN persistence for 3 months; (III) PSNs ≤30 mm and solid component ≤5 mm	2009–2011	Mean: 4.3±2.5 years, median: 3.5 [2.4–6.0] years	(I) Increase in maximal diameter ≥2 mm; (II) appearance of solid component; (III) increase in solid component ≥2 mm	2-year probabilities of growth: pure GGNs 2%, heterogeneous GGNs 12%, PSNs 17%. 5-year probabilities of growth: Pure GGNs 14%, heterogeneous GGNs 24%, PSNs 28%	Among resected SSNs: >400 days	91 nodules: 6 AAH; 33 AIS; 40 MIA; 12 invasive ADC	Initial maximal diameter

Table 2 *(continued)*

Table 2 *(continued)*

Study	No. of patients/ SSNs	Inclusion criteria	Enrollment duration	Follow-up duration	Definition of growth	SSNs with growth	Volume doubling time	No. of nodules with pathological confirmation	Factors related to SSN growth
Lee, 2016 (34)	213/213; 136: pure GGNs; 77: pSNs	(I) SSNs; (II) diameter of 5 mm to 3 cm; (III) solid portions within SSNs (if any) ≤5 mm	2005–2013	Median 849 [90–2,900] days	(I) Increase in diameter ≥2 mm; (II) solid portions in part-solid GGNs increased by ≥2 mm; (III) new solid portions developed within pure GGNs	42/213 (19.7%)	–	58 nodules: 9 AAH; 30 AIS; 5 MIA; 14 invasive ADC	Lung cancer history, PSNs, initial diameter
Sato, 2017 (35)	187 patients (78: multiple GGNs; 109: single GGN)	(I) Pure GGNs + PSNs; (II) diameter ≤3 cm; (III) GGO proportion ≥50%; (IV) observation without treatment for ≥6 months	2008–2014	Median 45.5 [24.9–87.0] months	(I) Gross increase in greatest dimension by ≥2 mm; (II) gross increase in solid component size by ≥2 mm; (III) new solid part of any size	At 36 months: 49/187 (26.2%); after 36 months: 13/187 (7.0%)	–	32 nodules: 2 not available; 5 AAH/AIS/MIA; 25 invasive ADC	Multiple GGNs: GGN size ≥10 mm, lung cancer history. Single GGN: partly solid pattern, GGN size ≥10 mm
Sawada, 2017 (36)	226 patients. No. of lesions (1: 168 patients; 2: 34 patients; 3: 18 patients; ≥4: 6 patients)	(I) Pure GGNs + PSNs; (II) diameter ≤3 cm	2000–2005	124 patients underwent resection: median 9.4 [2.9–100.5] months. Remaining 102 patients: (I) 57 patients: median 6.7 [9.6–167.5] months; (II) 45 patients: median 142.2 [87.7–200.9] months	(I) Increase in tumor size; (II) increase in consolidation tumor ratio (maximum diameter of consolidation relative to maximum tumor diameter)	39/226 (17.3%)	–	124 patients: 63 AIS; 36 MIA; 19 lepidic-predominant ADC; 5 papillary-predominant ADC; 1 acinar ADC	-
Lee, 2019 (37)	160/208	(I) Pure GGNs + PSNs; (II) size ≤3 cm without limitation concerning solid part ratio; (III) stable without resection for the first 5 years	2003–2017	Median 136 [120–179] months	(I) Increase in diameter ≥2 mm; (II) interval increase in diameter combined with development of new solid component	27/208 (13.0%)	–	3 nodules: 1 AIS; 1 MIA; 1 invasive ADC	History of cancer other than lung cancer, development of new solid component, bubble lucency
Lee, 2020 (38)	235/235; 211: pure GGNs; 24: PSNs	(I) SSNs with size ≥6 mm; (II) stable for 5 years after detection; (III) CT follow-up intervals for target SSNs aged ≥7 years; (IV) mean SSN diameter of 6–30 mm; (V) patient age ≥35 years	2002–2018	Median 112 [84–208] months	(I) Increase in mean diameter of entire nodule ≥2 mm; (II) solid portion increase in PSNs ≥2 mm; (III) new occurrence of solid portions within SSNs	5/235 (2.1%)	–	7 nodules: 1 AAH; 1 AIS; 5 invasive ADC	–
Qi, 2021 (39)	84/95	(I) Pure GGNs + PSNs; (II) pathologically confirmed SSNs with preoperative follow-up interval of ≥2 years; (III) follow-up interval of <2 years with pathologically confirmed SSNs that exhibited growth	2012–2021	Mean 42.1±17.0 months	(I) Volume increase ≥20%; (II) new development of solid components	Pure GGNs: 9.1% developed PSNs, 62.1% developed growth of GGO portion, PSNs: 87.5% growth in volume	Mean: 1,704.7±1,493.7 days	6 benign; 1 AAH; 9 AIS; 32 MIA; 47 invasive ADC	Initial volume

The data are expressed as mean ± standard deviation or median [interquartile range]. †, GGNs with a solid component in only the lung window but not in the mediastinal window. SSN, subsolid nodule; GGN, ground-glass nodule; PSN, part-solid nodule; GGO, ground-glass opacity; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; ADC, adenocarcinoma; AAH, atypical adenomatous hyperplasia.

that were absent at the initial evaluation and detected during follow-up. SSNs identified on follow-up rounds are more likely to resolve, compared with SSNs identified at baseline. In the International Early Lung Cancer Action Project, 66% of new GGNs and 70% of new PSNs decreased or resolved (46,47). In the NELSON trial, <1% of LDCT lung cancer screening participants developed a new SSN after the baseline evaluation. New SSNs that appear on follow-up examinations in patients without malignancy are more likely to be transient, considering the indolent nature of SSNs and long VDTs. In contrast to new solid nodules (48), new SSNs may not require more aggressive follow-up (49). A Korean study analyzed 6,725 screening-detected SSNs (5,241 SSNs detected at baseline screening and 1,484 newly detected SSNs on follow-up scans) (50). The authors found that newly observed SSNs during follow-up had a significantly lower probability of overall nodule growth [odds ratio =0.39, 95% confidence interval (CI) =0.26–0.59] and higher probability of resolution (odds ratio =6.30, 95% CI =5.09–7.81), compared with SSNs detected at baseline. Newly found SSNs also had a lower risk of undergoing biopsy (hazard ratio =0.39, 95% CI =0.26–0.51) and receiving a diagnosis of lung cancer (hazard ratio =0.31, 95% CI =0.19–0.51), compared with SSNs found at baseline. The authors of that study attributed these findings to the inflammatory nature of SSNs. Based on the results of recent studies, less aggressive follow-up and management may be appropriate for newly detected SSNs.

Genetic alterations in lung adenocarcinoma manifesting as SSNs

In previous studies of genetic alterations in lung adenocarcinoma manifesting as SSNs, *EGFR* mutations were the major driver mutations (frequency of 36–89%) (11,51-55). The differences in *EGFR* mutation frequency among these studies may be partly explained by differences in study populations (Asian *vs.* Caucasian), detection methods (polymerase chain reaction *vs.* next generation sequencing), and nodule subtypes (pure GGNs *vs.* PSNs). Other genetic alterations identified in lung adenocarcinoma manifesting as SSNs included *KRAS* mutations, *HER2* mutations, *BRAF* mutations, *ALK* rearrangement, and *ROS1* rearrangement (11,53-58).

The expression of programmed death ligand-1 (PD-L1) is low in SSNs (59,60). Suda *et al.* (59,60) found that the frequency of PD-L1 positivity was significantly higher in pure-solid lung adenocarcinomas than in part-solid lung adenocarcinomas (25% *vs.* 4%, P<0.01). Toyokawa *et al.* (60) reported that the frequency of PD-L1 positivity was significantly lower in lung adenocarcinomas with surrounding GGOs than in lung adenocarcinomas without surrounding GGOs (10% *vs.* 29%, P<0.01).

Preoperative evaluation of SSNs

Surgical resection is the preferred treatment for SSNs. In this section, we summarize the need for preoperative evaluation before surgical resection of SSNs.

PET/CT and brain magnetic resonance imaging (MRI)

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has limited utility in the diagnosis and staging of SSNs, compared with other solid nodules. Kim *et al.* (61) reported a high false-negative rate when using FDG-PET for the detection of bronchioloalveolar carcinoma, now known as AIS. In another study, Chun *et al.* (62) compared the maximum standardized uptake (SUV_{max}) values of inflammation and malignancy that manifested as GGN on chest CT. In mixed GGNs (PSNs), the SUV_{max} was significantly higher in inflammatory lesions (2.00±1.18) than in malignancies (1.26±0.71). However, in pure GGNs, both inflammation and malignancy showed similar SUV_{max} values of <1.0. Therefore, PET/CT is not recommended for the diagnosis of SSNs.

Cho *et al.* (63) evaluated the utilities of preoperative PET/CT and MRI in 164 lung adenocarcinomas with pure GGNs; they didn't find mediastinal or distant metastasis. We also evaluated the utilities of preoperative PET/CT and brain MRI in 35 pure GGNs and 39 PSNs; we found no mediastinal or distant metastases (64). Therefore, preoperative PET/CT and brain MRI are not useful for patients with pure GGNs. However, large-scale prospective studies are needed to determine the utilities of preoperative PET/CT and brain MRI in patients with PSNs, considering its more aggressive course.

CT-guided biopsy

A meta-analysis showed that CT-guided percutaneous biopsy for SSNs had high diagnostic sensitivity (92%, 95% CI =84–98%) and specificity (94%, 95% CI =84–98%), although sample sizes were small (n<90) in the included studies (n=6) (65). However, the diagnostic performance

was lower for SSNs with a size <10 mm and a greater proportion of ground-glass components (66). CT-guided percutaneous biopsy is associated with various complications, such as hemoptysis, pneumothorax, and air embolism (67). Additionally, a negative biopsy result does not exclude the possibility of malignancy. The Fleischner Society guidelines address that the appropriate use of invasive diagnostic and therapeutic procedures for pulmonary nodules is vitally important but depends greatly on available resources and expertise (68). Therefore, considering the potential limitations of CT-guided biopsy for SSNs such as inadequate sampling and false-negative results, in our institution surgical resection for peripheral SSNs is preferred over CT-guided biopsy.

Bronchoscopy

We previously evaluated the utility of preoperative flexible bronchoscopy in 264 patients with 296 SSNs; only 3 (1%) SSNs were preoperatively identified as malignant according to bronchial washing cytology (69). Therefore, bronchial washing is not recommended for diagnosis because of its low diagnostic yield. Preoperative flexible bronchoscopy has limited value for peripheral SSNs, which could be easily removed by sublobar resection.

Transbronchial lung biopsy with radial probe endobronchial ultrasound or virtual bronchoscopic navigation may be considered for the preoperative histological confirmation of SSNs that are located in the centers of lobes and require lobectomy. In previous meta-analyses, the pooled diagnostic yield of transbronchial lung biopsy was 75–81% (70-72).

Clinical guidelines for the surveillance of incidentally detected and screening-detected SSNs

Current guidelines regarding the management of SSNs include guidelines for incidentally detected nodules from the American College of Chest Physicians (ACCP) (73,74), British Thoracic Society (BTS) (75), and the Fleischner Society (68,76), as well as National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer (NSCLC) (77) (*Table 3*). Additionally, the guidelines for screening-detected nodules include guidelines from the Japanese Society for CT Screening (78), lung imaging reporting and data system (Lung-RADS) (79), and NCCN guidelines for lung cancer screening (80) (*Table 3*).

Because 60–70% of SSNs may be transient, the ACCP, BTS, and Fleischner Society guidelines recommend confirming that SSNs are persistent (68,73,75). The ACCP Consensus Asian Guidelines suggest that empirical antibiotics may be appropriate for PSNs with a size >8 mm (74).

Nodule growth is defined as a change in size of ≥2 mm in the BTS guidelines (75) and ≥1.5 mm in Lung-RADS 2022 (79) and NCCN guidelines (80). Nodule progression may manifest as a new or increasing solid component, or a uniform increase in attenuation (81). All guidelines recommend active surveillance and intervention for SSNs with interval progression.

Incidentally detected SSNs

According to the ACCP and BTS guidelines, follow-up is recommended for incidentally detected SSNs with a size >5 mm (73,75). However, the ACCP clinical practice consensus guidelines for Asia recommend surveillance for SSNs of all sizes because of the increased risk of malignancy in this population (74). The BTS guidelines recommend resection or nonsurgical treatment for SSNs that exhibit growth or altered morphology, including a new or increased solid component at the 3-month surveillance visit; the guidelines also recommend CT surveillance, image-guided biopsy, resection, or nonsurgical treatment for SSNs that are unchanged at the 3-month surveillance visit and have a high risk of malignancy (>10%) on the basis the Brock risk prediction model, which was also validated for SSNs (75,82).

Screening-detected SSNs

In contrast to the incidentally detected SSNs, there is no size threshold for follow-up of screening-detected SSNs (78-80). In Lung-RADS (version 1.1), a pure GGN with a size ≥30 mm that is unchanged or growing slowly is classified as category 2 (i.e., malignancy risk of <1%) (79). As previously discussed, 25–50% of resected pure GGNs exhibit invasive component in the histopathology (23-27). Therefore, Lung-RADS (version 1.1) underestimates the malignancy risk for slow-growing pure GGNs with a size ≥30 mm and makes no recommendations regarding tissue sampling for pure GGNs. However, the NCCN guidelines recommend biopsy or surgical excision for ≥20 mm pure GGNs that exhibit growth of >1.5 mm (80). Lung-RADS (version 1.1) and the NCCN guidelines recommend PET/CT and/or tissue sampling for PSNs with solid component size ≥6 mm and new/growing (>1.5 mm in

Table 3 Comparison of current guidelines for management of SSNs

Guidelines, year	Target population	Nodules requiring imaging follow-up	Initial imaging interval from baseline	Follow-up intervals	Conditions for further interventions	Surveillance endpoint for stable lesions
Guidelines for incidental nodules						
ACCP, 2013 (73)	SSNs	(I) GGNs >5 mm; (II) PSNs of any size: PSNs >15 mm may proceed directly to PET, nonsurgical biopsy, and/or surgical resection	(I) Annual surveillance: GGNs >5 mm; (II) 3-month surveillance: GGNs >10 mm and PSNs of any size	Annual surveillance: stable GGNs >5 mm; stable PSNs ≤8 mm	(I) Persistent GGN: size >10 mm may proceed to nonsurgical biopsy and/or surgical resection. Growth or development of solid component may warrant further evaluation and/or consideration for resection. (II) Persistent PSN: growth or solid component development requires further evaluation and/or consideration for resection, size >8 mm should proceed to PET, nonsurgical biopsy, and/or resection. PET may be used if solid component size >8 mm	(I) ≥3 years; (II) limited or no follow-up may be preferred by patients with life-limiting comorbidities, or patients who prefer to avoid treatment for potentially indolent lung cancers
BTS, 2015 (75)	(I) SSNs; (II) age ≥18 years	SSN ≥5 mm	3-month follow-up	Surveillance at 1, 2, and 4 years from baseline. Stable SSNs with low risk of malignancy (<10%)[†]	(I) Persistent stable SSNs at 3-month surveillance visit with higher risk of malignancy (>10%)[†] should proceed to CT surveillance, image-guided biopsy, or resection/nonsurgical treatment, based on patient preference; (II) increase in GGN size >2 mm. Consider resection/nonsurgical treatment or surveillance; (III) growth or altered morphology, including new/increased solid component at 3-month surveillance visit. Resection or nonsurgical treatment favored over observation	4 years
ACCP Consensus Guidelines for Asia, 2016 (74)	SSNs	(I) GGNs >5 mm: consider annual surveillance for nodules <5 mm after discussion with patient; (II) PSNs of any size	(I) Annual surveillance: any GGN; (II) 3-month surveillance: any PSN; consider empiric antimicrobial therapy for PSNs >8 mm if signs of bacterial infection at detection; (III) for PSNs >8 mm, immediate intervention should be considered if 3 months of surveillance may delay definitive diagnosis	Annual surveillance: stable GGNs >5 mm and discussion of active surveillance for GGNs ≤5 mm. Stable PSNs ≤8 mm	Persistent PSNs >8 mm: further evaluation with nonsurgical biopsy or surgical resection. PET may be considered for staging before surgical intervention	(I) ≥3 years for nonsolid nodules >5 mm. Consider ongoing annual surveillance beyond 3 years; (II) Pure GGNs <5 mm: consider annual surveillance according to clinical judgement and patient preference
Fleischner Society, 2017 (68,76)	(I) SSNs; (II) age ≥35 years; (III) no active malignancy; (IV) non-immunocompromised	(I) SSNs >6 mm; (II) multiple SSNs at baseline may consider follow-up at 2 and 4 years for suspicious pure GGNs <6 mm	(I) 6–12 months: GGNs >6 mm; (II) 3–6 months: PSNs >6 mm, multiple SSNs	(I) Every 2 years: stable GGNs, consider for multiple persistent GGNs <6 mm in high-risk patients; (II) annual: stable PSNs	(I) Persistent GGN: consider resection if growth or solid component develops; (II) persistent PSN: solid components >6 mm highly suspicious for invasive pathology; (III) nodules with suspicious morphology (lobular, bubble lucency), growing solid component, or solid component >8 mm may proceed to PET, biopsy or resection	≥5 years
NCCN guidelines for NSCLC, 2022 (77)	Incidentally detected SSNs	(I) SSN ≥6 mm; (II) multiple SSNs	(I) 6–12 months: GGNs ≥6 mm; (II) 3–6 months: PSNs ≥6 mm and multiple SSNs	(I) Every 2 years: stable GGNs ≥6 mm and stable multiple SSNs <6 mm; (II) annual: stable PSNs ≥6 mm	(I) PET/CT or biopsy: PSN solid component size ≥6 mm	5 years

Table 3 *(continued)*

Table 3 *(continued)*

Guidelines, year	Target population	Nodules requiring imaging follow-up	Initial imaging interval from baseline	Follow-up intervals	Conditions for further interventions	Surveillance endpoint for stable lesions
Guidelines for screening-detected nodules						
Japanese Society for CT Screening, 2013 (78)	SSNs	All SSNs: (I) GGNs <15 mm; (II) PSNs <15 mm and solid component size ≤5 mm	3 months	12 and 24 months	(I) GGNs ≥15 mm; (II) PSNs <15 mm and solid component size >5 mm or PSNs ≥15 mm; (III) size increase or solid component size >5 mm; (IV) solid component size ≤5 mm, based on hospital guidelines	NA
ACR, Lung-RADS 2022, 2022 (79)	(I) Age: 55 years; (II) upper age limit: 77 years per Centers for Medicare and Medicaid Services; 80 years per US Preventive Services Task Force; (III) no active symptoms of lung cancer; (IV) smoking history of ≥30 pack-years; (V) current smoker or quit smoking within 15 years	Annual surveillance implied	(I) Annual surveillance (Lung-RADS 2): pure GGNs <30 mm; PSNs <6 mm; (II) 6-month surveillance (Lung-RADS 3): GGNs ≥30 mm at baseline; PSNs ≥6 mm; (III) 3-month surveillance (Lung-RADS 4A): PSN, solid component of 6–8 mm	(I) Annual surveillance: Lung-RADS 1 or 2; (II) 6-month surveillance (Lung-RADS 3): new SSNs; (III) 3-month surveillance (Lung-RADS 4A): PSNs with new/growth of solid component <4 mm	PET/CT (if solid component size ≥8 mm) and/or tissue sampling depending on malignancy risk and comorbidities, and patient preference (Lung-RADS 4B): solid component ≥8 mm or new/growing solid component ≥4 mm	(I) Age; (II) life-limiting comorbidity
NCCN guidelines for lung cancer screening, 2022 (80)	Age ≥50 years and smoking history of ≥20 pack-years	Annual surveillance implied	(I) Annual surveillance: GGNs <20 mm; PSNs <6 mm; (II) 6-month surveillance: GGNs ≥20 mm; PSNs ≥6 mm and solid component size <6 mm; (III) 3-month surveillance or PET/CT: PSNs ≥6 mm and solid component size 6–8 mm; (IV) contrast-enhanced chest CT and/or PET/CT: PSN solid component size ≥8 mm	(I) Annual surveillance: new (<20 mm) or stable GGN: stable PSNs <6 mm; stable PSNs ≥6 mm with solid component size <6 mm; (II) 6-month surveillance: new GGNs ≥20 mm (if stable, annual LDCT possible); growing GGN (>1.5 mm) with size <20 mm; new PSNs <6 mm; stable PSNs ≥6 mm with solid component size 6–8 mm (or PET/CT); (III) 3-month surveillance: new/growing PSN ≥6 mm with solid component growth of <4 mm	(I) Contrast-enhanced chest CT and/or PET: new/growing PSN with solid component size ≥4 mm; (II) PET: stable PSNs ≥6 mm and solid component size 6–8 mm; (III) consider biopsy or surgical excision: GGNs with growth (>1.5 mm) and size ≥20 mm: high suspicion of lung cancer after PET/CT; stable PSN with solid component size >8 mm	Until patient is no longer a candidate for definitive treatment
Samsung Medical Center guidelines*	Incidental- or screening-detected SSNs	SSNs of all sizes	3-month follow-up	(I) Annual surveillance: pure GGNs <15 mm; (II) 6-month surveillance: pure GGNs ≥15 mm; PSN solid component size <6 mm and total size <15 mm	(I) Persistent pure GGN: ≥15 mm may proceed to surgical resection (preferred) or nonsurgical biopsy; growth or development of solid component may warrant further evaluation and/or consideration for resection; (II) persistent PSN: growth in size or solid component requires further evaluation and/or consideration for resection; solid component size ≥6 mm or total size ≥15 mm requires resection (preferred) or nonsurgical biopsy	≥5 years

*, Samsung Medical Center: a 1979-bed referral hospital in Seoul, Korea; †, malignancy risk was assessed using the Brock model and morphology (solid component size, pleural indentation, and bubble lucency), along with factors such as smoking history and lung cancer history. SSN, subsolid nodule; ACCP, American College of Chest Physicians; BTS, British Thoracic Society; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; CT, computed tomography; ACR, American College of Radiology; Lung-RADS, lung imaging reporting and data system; GGN, ground-glass nodule; PSN, part-solid nodule; PET, positron emission tomography; LDCT, low-dose helical computed tomography; NA, not available.

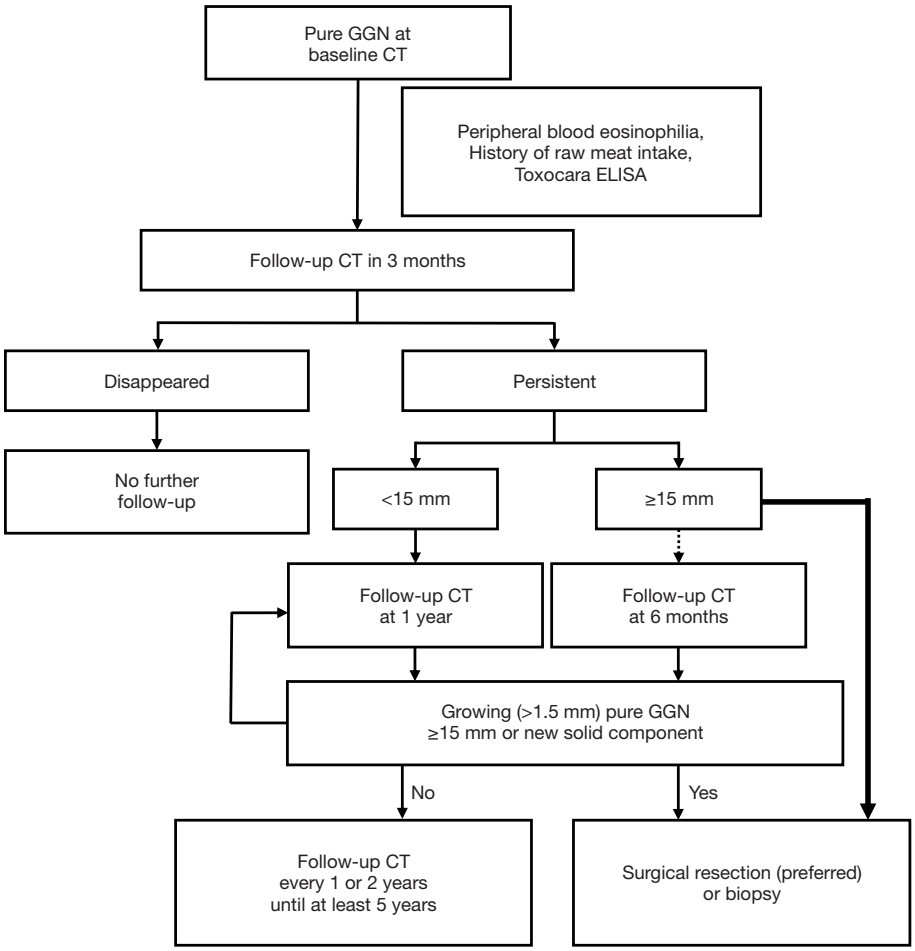

Figure 2 Samsung Medical Center guidelines for the surveillance of pure GGNs. Bold lines indicate preferred options. GGN, ground-glass nodule; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay.

solid component) PSNs with solid component size ≥4 mm (79,80). The Japanese Society for CT Screening guidelines (version 3) recommend surgical resection or nonsurgical biopsy for pure GGNs or PSNs with a size ≥15 mm and for PSNs of all sizes with a solid component size >5 mm (78). Notably, the Japanese Society for CT Screening guidelines recommend biopsy or surgery for smaller PSNs (even if the solid component is ≤5 mm) based on the physician's discretion, presumably because of the greater risk of SSN malignancy in the East Asian population (83).

Surveillance endpoint for stable SSNs

Table 3 summarizes the surveillance endpoint for stable SSNs. For stable incidental SSNs, the 2013 ACCP guidelines recommend ≥3 years of surveillance (73); however, the recent Fleischner Society guidelines recommend ≥5 years of surveillance (68). However, for screening-detected SSNs, the NCCN guidelines recommend surveillance until the patient is no longer a candidate for definitive treatment (77). Overall, long-term follow-up studies (i.e., >15 years) are needed to determine the optimal follow-up duration for stable SSNs.

Our institutional surveillance guidelines for pure GGNs and PSNs

Our multidisciplinary pulmonary nodule management team, which includes pulmonologists, radiologists, and thoracic surgeons, developed institutional guidelines for SSNs in 2018 (*Table 3*, *Figures 2,3*). Our institutional guidelines make same recommendations for both screening- and incidentally

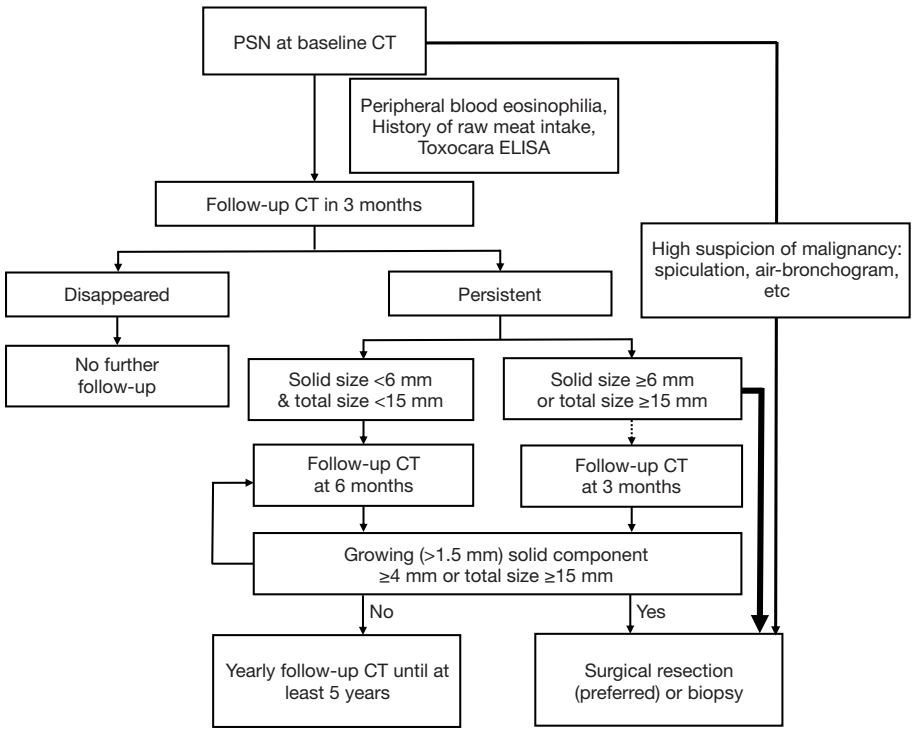

Figure 3 Samsung Medical Center guidelines for the surveillance of PSNs. Bold lines indicate preferred options. PSN, part-solid nodule; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay.

detected SSNs. Considering the high prevalence of pulmonary toxocariasis in our country (20), newly detected SSNs are followed up with a 3-month chest CT, blood serology (*Toxocara* enzyme-linked immunosorbent assay), and questions regarding raw meat intake. We do not use a minimum size threshold for follow-up because of our experience concerning pure GGNs with a baseline size of 4–5 mm that grew during long-term follow-up and were finally diagnosed as adenocarcinoma (10). Similar to the Japanese Society for CT Screening guidelines, our institutional guidelines recommend a total size threshold of ≥15 mm, rather than ≥20 mm, for the surgical resection of persistent pure GGNs, based on the extent of sublobar lung resection, as well as radiation exposure and patient anxiety during CT surveillance (*Figure 2*). Surgery is also indicated for growing (>1.5 mm) pure GGN with a total size of ≥15 mm or pure GGN with a new solid component during follow-up. Additionally, a study conducted at our institution revealed that GGNs with a nodule size >16.4 mm were associated with IA (23). Surgery is indicated for persistent PSNs with a total size of ≥15 mm or solid component size of ≥6 mm (*Figure 3*). Furthermore, surgery is indicated for PSNs with a solid component size ≥4 mm that exhibit solid component growth of >1.5 mm and for growing PSNs with total size of ≥15 mm during follow-up. We also recommend ≥5 years of follow-up for both pure GGNs and PSNs.

Role of artificial intelligence (AI) tools in SSNs

AI is computer science concerned with developing systems that can perform tasks that typically require human intelligence, such as problem-solving, reasoning, and perception (84,85). These days, AI technology has developed and is also applied in many medical fields. AI advancements might help physicians detect and diagnose pulmonary nodules (86). Many deep learning algorithms showed high sensitivity (around 70–91%), and all physicians showed improvement in lung nodule detection performance with the assistance of these algorithms (87,88). Some studies suggested that diagnostic models could be developed to differentiate benignancy and malignancy in GGNs (89-91). They reported that several models showed different diagnostic performances; however, their best models showed an area under the curve (AUC) value around

0.73–0.92 to differentiate benign and malignant GGNs (89-91). They also suggested that deep learning models can assist radiologists in determining benign and malignant GGNs (89). Our group also investigated the possibility of deep learning analysis to predict *EGFR* mutation status in lung adenocarcinoma manifesting as pGGNs (92). In our study, the AUC of the clinical only and deep learning with clinical models to predict *EGFR* mutations were 0.50 and 0.85, respectively. We suggested that a deep learning approach of CT images combined with clinical factors can predict *EGFR* mutations in pGGNs.

Surgical treatment of SSNs

Table 4 presents the results of studies concerning overall survival (OS) and relapse-free survival (RFS) in patients with SSNs (93-99). Multiple retrospective studies have demonstrated excellent outcomes of surgical resection for SSNs, with a 5-year survival rate >95%. In a previous study conducted at our institution, the GGO-dominant clinical stage IA lung adenocarcinoma (pure GGO group) had an excellent prognosis after wedge resection (95). Radiological noninvasiveness (C/T ratio ≤0.25) was a good indicator of suitability for sublobar resection in patients with early-stage lung cancer. However, wedge resection should be carefully considered for patients with mixed GGNs (PSNs) (C/T ratio >0.25) because of the high recurrence rate (95). A recent Japanese single-arm study showed that sublobar surgical resection, including both wedge resection and segmentectomy, with a sufficient surgical margin was feasible and effective for the treatment of GGO-dominant peripheral lung cancer with a size ≤2 cm and C/T ratio ≤0.25 (JCOG0804/WJOG4507L) (98). The 5-year RFS was 99.7% and there were no instances of recurrence (98). Another recent Japanese multicenter, phase 3, randomized, controlled, noninferiority trial (JCOG0802/WJOG4607L) showed improved OS after segmentectomy, compared with lobectomy, for patients who had small peripheral NSCLCs with a diameter ≤2 cm and C/T ratio >0.5 (99). During a median follow-up interval of 7.3 years, the 5-year OS rates were 94.3% for segmentectomy and 91.1% for lobectomy. The 5-year RFS rates were 88.0% for segmentectomy and 87.9% for lobectomy. Although 51% of the patients had solid nodules with a C/T ratio of 1, the results suggest that segmentectomy should be the standard surgical procedure for small peripheral tumors with a diameter ≤2 cm and C/T ratio >0.5. Most recently, results of the CALGB 140503 trial have been announced (100). CALGB 140503 trial is a multicenter international non-inferiority phase III trial in which NSCLC patients clinically staged as T1aN0 with tumor size ≤2 cm were randomly assigned to sublobar or lobar resection. This trial show that for patients with peripheral NSCLC with 2 cm or less in tumor size who have pathologically confirmed node-negative disease, sublobar resection is non-inferior to lobectomy. For RFS, the stratified HR was 0.999 (95% CI, 0.784–1.272). For OS the stratified HR was 0.930 (95% CI, 0.695–1.243).

Nonsurgical treatment options for SSNs

Multiple nonsurgical treatment options are available for SSNs. Combinations of surgical and nonsurgical treatment are also useful, particularly for multifocal SSNs.

Stereotactic body radiotherapy (SBRT)

SBRT is an alternative treatment option for SSNs, particularly in older patients with multiple comorbidities (101). If a growing PSN is located centrally and lobectomy is necessary in an older patient with multiple comorbidities, SBRT should be considered because the rate of lobectomy-related mortality is approximately 2–4% in patients aged >70 years (102-104). Although SBRT is commonly performed as treatment for SSNs, data regarding SBRT are scarce. Hammer *et al.* (105) recommended the use of SBRT for nonsolid Lung-RADS 4B/4X nodules in patients aged >77 years and the use of surgery for such nodules in patients aged ≤77 years. SBRT was associated with the longest OS (80%), followed by surgery (79%; 49,139 of 62,559 patients) and no treatment (74%, P<0.01). Therefore, in the situations where surgical risk is high (for example, older patients with multiple comorbidities who need lobectomy, patients with reduced pulmonary function due to severe chronic obstructive pulmonary disease or diffuse interstitial lung disease, etc.), the treatment decision of SBRT *vs.* surgery needs to be made after multidisciplinary team discussion.

Radiofrequency ablation (RFA)

RFA is used for the ablation of solid organs and is a newer treatment option for medically inoperable primary lung cancer. RFA is regarded as an alternative treatment option for SSNs. Iguchi *et al.* (106) reported the clinical outcomes of RFA for 16 patients with lung cancer and a GGO component of >50%. Although there were no

Table 4 Comparison of the results of studies according to surgical treatment of SSNs

Study	Study design	No. of patients	Inclusion criteria	Registration duration	Follow-up duration	Results
Asamura, 2013 (93)	Multicenter (31 institutions), prospective (JCOG 0201)	Total (n=545)	(I) Clinical stage IA NSCLC; (II) located peripherally in outer half of lung field; (III) C/T ratios of 0.50 for cT1a-b (≤3.0 cm) and 0.25 for cT1a (≤2.0 cm)	December 2002 to May 2004	Median 7.1 [0.0–8.5] years	5-year OS: all patients (90.6%); C/T ratios of 0.50 for cT1a-b (≤3.0 cm) (88.9%); C/T ratios of 0.25 for cT1a (≤2.0 cm) (96.7%) (P<0.001). 5-year RFS: all patients (84.7%); C/T ratios of 0.50 for cT1a-b (≤3.0 cm) (92.4%); C/T ratios of 0.25 for cT1a (≤2.0 cm) (97.1%) (P=0.259)
Tsutani, 2014 (94)	Multicenter, retrospective	Total (n=239): wedge resection (n=93); segmentectomy (n=56); lobectomy (n=90)	(I) T1N0M0, stage IA ADC; (II) GGO-dominant tumor (>50% GGO component)	August 2005 to January 2010	Median: 42.4 months after surgery	3-year OS (P=0.56): wedge resection (100%); segmentectomy (100%); lobectomy (95.9%). 3-year RFS (P=0.66): wedge resection (100%); segmentectomy (92.9%); lobectomy (93.7%)
Cho, 2015 (95)	Single center, retrospective	Total (n=97): pure GGN (n=71); PSN (n=26)	(I) Stage IA ADC; (II) SSN (C/T ratio ≤0.25, pure GGN group; C/T ratio >0.25, PSN group); (III) wedge resection	2004–2010	Mean 44.7 (range, 5–93) months	5-year OS (P=0.663): 98.6% in GGNs; 95.5% in PSNs. 5-year RFS (P=0.003): 100.0% in GGNs; 85.0% in PSNs
Ye, 2018 (96)	Single center, retrospective	Total (n=841): pure GGN (n=534), PSN (n=307); wedge resection (n=474), segmentectomy (n=89), lobectomy (n=278)	(I) ADC; (II) maximum tumor diameter ≤3 cm	January 2008 to December 2014	Median 38 [3–89] months	5-year lung cancer-specific OS: 98.99%. 5-year lung cancer-specific RFS: 95.76%
Miyoshi, 2019 (97)	Single center, retrospective	465 nodules with GGO component	(I) Pathological stage IA ADC; (II) underwent lobectomy and systemic lymph node dissection	2003–2014	Median 79 [49–117] months	5-year OS: 97%
Suzuki, 2022 (98)	Multicenter (51 institutions), single-arm confirmatory trial (JCOG0804/WJOG4507L)	Total (n=325): sublobar resection (n=314); conversion to lobectomy (n=11)	(I) Radiologically suspicious lung cancer; (II) ≤3 bilateral or unilateral lesions; (III) center of tumor located in outer third of lung field; (IV) no nodal involvement; (V) maximum tumor diameter ≤2.0 cm; (VI) C/T ratio ≤0.25	May 2009 to April 2011	Median: 5.5 years	5-year OS: 99.4% (97.5–99.8%) after sublobar resection. 5-year RFS: 99.7% (98.3–99.9%) after sublobar resection. No differences in survival between wedge resection and segmentectomy
Saji, 2022 (99)	Multicenter (70 institutions), open-label, phase 3, randomized, controlled, noninferiority trial (JCOG0802/WJOG4607L)	Segmentectomy (n=552); lobectomy (n=554)	(I) Clinical stage IA NSCLC; (II) tumor diameter ≤2 cm; (III) C/T ratio >0.5*; (IV) located in outer third of pulmonary parenchyma	August 2009 to August 2014	Median 7.3 [0.0–10.9] years	5-year OS: segmentectomy [94.3% (92.1–96.0%)]; lobectomy [91.1% (88.4–93.2%)] [hazard ratio =0.663 (0.474–0.927), one-sided P<0.0001 for noninferiority, P=0.0082 for superiority]. 5-year RFS: segmentectomy [88.0% (85.0–90.4%)]; lobectomy [87.9% (84.8–90.3%)]; [hazard ratio =0.998 (0.753–1.323), P=0.9889]. Local relapse: segmentectomy (10.5%); lobectomy (5.4%) (P=0.0018)

The data are expressed as median [interquartile range]. *, protocol was revised 4 years after initiation of enrollment to change eligibility criterion from C/T ratio of ≥0.25 to ≥0.5. Therefore, C/T ratio of ≤0.5 was used in this analysis. SSN, subsolid nodule; JCOG, Japan Clinical Oncology Group; WJOG, West Japan Oncology Group; GGN, ground-glass nodule; PSN, part-solid nodule; GGO, ground-glass opacity; NSCLC, non-small cell lung cancer; C/T, consolidation-to-tumor; ADC, adenocarcinoma; OS, overall survival; RFS, relapse-free survival.

major complications, pneumothorax occurred during 15 of 20 RFA sessions. During a median follow-up interval of 61.5 months, the 5-year OS and 5-year RFS rates were 93.3% and 100%, respectively (106). RFA was performed under local anesthesia in the outpatient setting, rather than under general anesthesia. However, lesions >3 cm should not be managed with RFA; the lesion location is also important because of the risk of damage to adjacent structures (e.g., esophagus and trachea) (107,108). Endobronchial ultrasound-guided bipolar RFA has also been described recently (109). Further studies are needed to identify good candidates for RFA treatment of SSNs and to identify the optimal delivery method for RFA (extrathoracic or endobronchial).

Medical treatments

Several medical treatment options for SSNs were previously evaluated. Lu *et al.* (110) evaluated the impact of platinum-based chemotherapy (cisplatin or carboplatin) on GGNs that persisted for ≥3 months. During follow-up, on a per-nodule basis, 86 (94.5%) GGNs had an unchanged size, and 5 (5.5%) GGNs increased in size. Considering the natural course of GGNs, chemotherapy had no effect on their growth (110). We hypothesized that lung adenocarcinoma with SSNs may respond to epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) because of the high frequency of *EGFR* mutations (89%) (54). Therefore, we investigated the impact of EGFR-TKIs (gefitinib or erlotinib) on concurrent SSNs in patients with stage IV NSCLC (111). In our retrospective study, almost 20% of concurrent SSNs with stage IV NSCLC shrank after EGFR-TKI treatment. Therefore, EGFR-TKI therapy may affect the natural course of SSNs. However, no study has directly evaluated the use of EGFR-TKIs in the treatment of SSNs, except for SSNs in patients with stage IV NSCLC. In situations where surgery or radiation therapy is not feasible because of multiplicity, location (lobe center), old age, multiple comorbidities, or patient refusal, EGFR-TKIs may be an appropriate therapeutic option for multiple growing SSNs. Further prospective studies are needed to determine the utility of EGFR-TKIs in the management of SSNs. An Italian group performed a phase IIb multicenter randomized study to assess the efficacy of low-dose aspirin in reducing SSN size (112), based on the successful use of aspirin in cancer prevention. The previous study showed an almost 30% reduction in lung cancer-related mortality after 5 years of aspirin treatment and 20 years of follow-up (113). However, in the Italian study, there was no change in the sum of the longest diameters of the target nodules in the placebo and low-dose aspirin groups after 12 months of treatment. The investigators suggested that the null result could be explained by the small study population and short study duration.

Management of multifocal SSNs

Multiple persistent SSNs often represent synchronous or metachronous lung primary cancer, rather than intrapulmonary metastases (114,115). Multiple SSNs often occur in women, never-smokers, and North American and Asian populations (115). Each lesion should be managed individually with intervention or surveillance, depending on the changes in overall size and solid component size over time. The Fleischner Society guidelines recommend follow-up CT at 3–6 months for multiple incidental SSNs with a size ≥6 mm; subsequent management should be based on the most suspicious nodule(s) (76).

Wang *et al.* (116) evaluated the clinical and pathological characteristics of 99 patients with single GGNs and 102 patients with multiple GGNs (>3 nodules). All patients with >10 nodules showed bilateral pulmonary nodules and presented with both pure and mixed GGNs. However, the proportions of mixed GGNs and malignant nodules significantly decreased as the total number of lesions increased (116). Sato *et al.* (35) investigated the natural history and clinical characteristics of multiple SSNs; they observed progression in 32% of patients at 36 months and 5% of patients after 36 months. Among patients with multiple SSNs who exhibited growth of a single SSN, 41% experienced residual SSN growth (35).

Kim *et al.* (117) reported the clinical outcomes of multiple pure GGNs after surgical resection. Five patients underwent resection of all GGNs, whereas 18 patients underwent resection of some GGNs and serial CT for the remaining lesions. No GGNs increased in size and no new solid component developed during a median follow-up interval of 40.3 months (range, 22–110 months) in 18 patients. The investigators suggested that, when it is unfeasible to resect all GGNs, CT-based close follow-up is an alternative to surgical resection. Hattori *et al.* (118) reported the outcomes of 53 patients who underwent surgical resection for multifocal SSNs (C/T ratio: 0–0.5). Regarding surgical managements for multifocal SSNs, the 5-year OS rates of multiple synchronous or staged limited resection alone *vs.* anatomical resection with or

without additional limited resection were similar. There were 278 resected multifocal SSNs, most of which had adenocarcinoma or AAH/AIS. Unresected or newly developed SSNs occurred in almost 36% of patients, and all of these SSNs remained stable as pure GGNs of size <10 mm without any intervention. The 5-year OS rates of multifocal SSNs and solid lesions were 94.4% and 80.6%, respectively, over a median follow-up interval of 60 months (118). Therefore, considering the outcomes of surgery for multiple SSNs, a reasonable approach may comprise lung-sparing limited resection for the most dominant lesion(s) and periodic CT surveillance for SSNs that remain after surgery.

Conclusions

The differential diagnoses of SSNs include benign and malignant lesions. Because a substantial proportion of SSNs tend to disappear, there is a need to confirm that SSNs are persistent before performing any invasive procedures. Even in patients with precancerous or cancerous lesions, the natural course of SSNs is generally indolent and the clinical outcomes are often favorable. However, PSNs may have a less indolent clinical course compared with pure GGNs; therefore, careful follow-up is necessary. Periodic CT surveillance and surgery are the main strategies for the management of persistent SSNs. For the preoperative evaluation of SSNs, PET/CT, brain MRI, and bronchoscopy have limited utility. The size, solidity, location, and number of SSNs are important factors in determining the need for surveillance, biopsy, and surgical resection, as well as the duration of follow-up. For SSNs, sublobar resection with sufficient surgical margins based on the C/T ratio is feasible and effective. Nonsurgical treatment options for SSNs include SBRT and RFA. The need for CT surveillance and surgical treatment of multifocal SSNs should be determined on the basis of the most dominant SSN(s). Combinations of surgical and nonsurgical treatment may also be useful, particularly for multifocal SSNs. Practice guidelines for the management of incidentally detected and screening-detected SSNs should be updated based on the accumulated knowledge regarding SSNs. Since the SSN is a heterogeneous disease, a personalized medicine approach is needed in the future. To this end, future studies of the SSNs should focus on their natural history, optimal follow-up duration, genetic features, surgical methods and nonsurgical treatments. All these information will pave the way to the personalized medicine approach for the SSNs.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5246/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5246/coif). SWU serves as an unpaid editorial board member of *Annals of Translational Medicine* from September 2022 to August 2024. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med 2020;41:1-24.
2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524-48.
3. ; Aberle DR, Adams AM, et al. Reduced lung-cancer

mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
4. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. J Thorac Oncol 2019;14:1732-42.
5. 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;382:503-13.
6. Kakinuma R, Muramatsu Y, Asamura H, et al. Low-dose CT lung cancer screening in never-smokers and smokers: results of an eight-year observational study. Transl Lung Cancer Res 2020;9:10-22.
7. Kang HR, Cho JY, Lee SH, et al. Role of Low-Dose Computerized Tomography in Lung Cancer Screening among Never-Smokers. J Thorac Oncol 2019;14:436-44.
8. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology 2013;266:304-17.
9. Migliore M, Fornito M, Palazzolo M, et al. Ground glass opacities management in the lung cancer screening era. Ann Transl Med 2018;6:90.
10. 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;143:172-8.
11. Kobayashi Y, Mitsudomi T, Sakao Y, et al. Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules: the differences between nodules with and without growth. Ann Oncol 2015;26:156-61.
12. Lee HY, Lee KS. Ground-glass opacity nodules: histopathology, imaging evaluation, and clinical implications. J Thorac Imaging 2011;26:106-18.
13. Infante M, Lutman RF, Imparato S, et al. Differential diagnosis and management of focal ground-glass opacities. Eur Respir J 2009;33:821-7.
14. Park CM, Goo JM, Lee HJ, et al. Focal interstitial fibrosis manifesting as nodular ground-glass opacity: thin-section CT findings. Eur Radiol 2007;17:2325-31.
15. Scholten ET, de Jong PA, de Hoop B, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? Eur Respir J 2015;45:765-73.
16. Oh JY, Kwon SY, Yoon HI, et al. Clinical significance of a solitary ground-glass opacity (GGO) lesion of the lung detected by chest CT. Lung Cancer 2007;55:67-73.
17. Yu JY, Lee B, Ju S, et al. Proportion and characteristics of transient nodules in a retrospective analysis of pulmonary nodules. Thorac Cancer 2012;3:224-8.
18. Jeong YJ, Kim KI, Seo IJ, et al. Eosinophilic lung diseases: a clinical, radiologic, and pathologic overview. Radiographics 2007;27:617-37; discussion 637-9.
19. Magnaval JF, Glickman LT, Dorchies P, et al. Highlights of human toxocariasis. Korean J Parasitol 2001;39:1-11.
20. Kang YR, Kim SA, Jeon K, et al. Toxocariasis as a cause of new pulmonary infiltrates. Int J Tuberc Lung Dis 2013;17:412-7.
21. 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;6:244-85.
22. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
23. Lim HJ, Ahn S, Lee KS, et al. Persistent pure ground-glass opacity lung nodules ≥ 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. Chest 2013;144:1291-9.
24. She Y, Zhao L, Dai C, et al. Preoperative nomogram for identifying invasive pulmonary adenocarcinoma in patients with pure ground-glass nodule: A multi-institutional study. Oncotarget 2017;8:17229-38.
25. Ichinose J, Kawaguchi Y, Nakao M, et al. Utility of Maximum CT Value in Predicting the Invasiveness of Pure Ground-Glass Nodules. Clin Lung Cancer 2020;21:281-7.
26. 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;107:904-10.
27. Xiang W, Xing Y, Jiang S, et al. Morphological factors differentiating between early lung adenocarcinomas appearing as pure ground-glass nodules measuring ≤10 mm on thin-section computed tomography. Cancer Imaging 2014;14:33.
28. Jang HJ, Lee KS, Kwon OJ, et al. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. Radiology 1996;199:485-8.
29. Gaeta M, Caruso R, Barone M, et al. Ground-glass attenuation in nodular bronchioloalveolar carcinoma: CT patterns and prognostic value. J Comput Assist Tomogr 1998;22:215-9.
30. Kobayashi Y, Fukui T, Ito S, et al. How long should small lung lesions of ground-glass opacity be followed? J Thorac Oncol 2013;8:309-14.

31. Matsuguma H, Mori K, Nakahara R, et al. Characteristics of subsolid pulmonary nodules showing growth during follow-up with CT scanning. Chest 2013;143:436-43.
32. 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;11:1453-9.
33. Kakinuma R, Noguchi M, Ashizawa K, et al. Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study. J Thorac Oncol 2016;11:1012-28.
34. Lee JH, Park CM, Lee SM, et al. Persistent pulmonary subsolid nodules with solid portions of 5 mm or smaller: Their natural course and predictors of interval growth. Eur Radiol 2016;26:1529-37.
35. Sato Y, Fujimoto D, Morimoto T, et al. Natural history and clinical characteristics of multiple pulmonary nodules with ground glass opacity. Respirology 2017;22:1615-21.
36. Sawada S, Yamashita N, Sugimoto R, et al. Long-term Outcomes of Patients With Ground-Glass Opacities Detected Using CT Scanning. Chest 2017;151:308-15.
37. 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;14:1370-7.
38. Lee JH, Lim WH, Hong JH, et al. Growth and Clinical Impact of 6-mm or Larger Subsolid Nodules after 5 Years of Stability at Chest CT. Radiology 2020;295:448-55.
39. Qi LL, Wang JW, Yang L, et al. Natural history of pathologically confirmed pulmonary subsolid nodules with deep learning-assisted nodule segmentation. Eur Radiol 2021;31:3884-97.
40. Kanashiki M, Tomizawa T, Yamaguchi I, et al. Volume doubling time of lung cancers detected in a chest radiograph mass screening program: Comparison with CT screening. Oncol Lett 2012;4:513-6.
41. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 2000;73:1252-9.
42. Hiramatsu M, Inagaki T, Inagaki T, et al. Pulmonary ground-glass opacity (GGO) lesions-large size and a history of lung cancer are risk factors for growth. J Thorac Oncol 2008;3:1245-50.
43. Kobayashi Y, Sakao Y, Deshpande GA, et al. The association between baseline clinical-radiological characteristics and growth of pulmonary nodules with ground-glass opacity. Lung Cancer 2014;83:61-6.
44. Liang X, Liu M, Li M, et al. Clinical and CT Features of Subsolid Pulmonary Nodules With Interval Growth: A Systematic Review and Meta-Analysis. Front Oncol 2022;12:929174.
45. Kaneda H, Nakano T, Taniguchi Y, et al. A decrease in the size of ground glass nodules may indicate the optimal timing for curative surgery. Lung Cancer 2014;85:213-7.
46. 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;207:1176-84.
47. Yankelevitz DF, Yip R, Smith JP, et al. CT Screening for Lung Cancer: Nonsolid Nodules in Baseline and Annual Repeat Rounds. Radiology 2015;277:555-64.
48. Walter JE, Heuvelmans MA, de Jong PA, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol 2016;17:907-16.
49. Walter JE, Heuvelmans MA, Yousaf-Khan U, et al. New Subsolid Pulmonary Nodules in Lung Cancer Screening: The NELSON Trial. J Thorac Oncol 2018;13:1410-4.
50. Kim YW, Kwon BS, Lim SY, et al. Lung cancer probability and clinical outcomes of baseline and new subsolid nodules detected on low-dose CT screening. Thorax 2021;76:980-8.
51. Aoki T, Hanamiya M, Uramoto H, et al. Adenocarcinomas with predominant ground-glass opacity: correlation of morphology and molecular biomarkers. Radiology 2012;264:590-6.
52. Dai J, Shi J, Soodeen-Lalloo AK, et al. Air bronchogram: A potential indicator of epidermal growth factor receptor mutation in pulmonary subsolid nodules. Lung Cancer 2016;98:22-8.
53. Choi Y, Kim KH, Jeong BH, et al. Clinicoradiopathological features and prognosis according to genomic alterations in patients with resected lung adenocarcinoma. J Thorac Dis 2020;12:5357-68.
54. Lee H, Joung JG, Shin HT, et al. Genomic alterations of ground-glass nodular lung adenocarcinoma. Sci Rep 2018;8:7691.
55. Li Y, Li X, Li H, et al. Genomic characterisation of pulmonary subsolid nodules: mutational landscape and radiological features. Eur Respir J 2020;55:1901409.
56. Zhao M, Zhan C, Li M, et al. Aberrant status and clinicopathologic characteristic associations of 11 target genes in 1,321 Chinese patients with lung adenocarcinoma. J Thorac Dis 2018;10:398-407.
57. Chen K, Chen W, Cai J, et al. Favorable prognosis and high discrepancy of genetic features in surgical patients with multiple primary lung cancers. J Thorac Cardiovasc

Surg 2018;155:371-379.e1.
58. Wei Z, Wang Z, Nie Y, et al. Molecular Alterations in Lung Adenocarcinoma With Ground-Glass Nodules: A Systematic Review and Meta-Analysis. Front Oncol 2021;11:724692.
59. Suda K, Shimoji M, Shimizu S, et al. Comparison of PD-L1 Expression Status between Pure-Solid Versus Part-Solid Lung Adenocarcinomas. Biomolecules 2019;9:456.
60. Toyokawa G, Takada K, Okamoto T, et al. Computed Tomography Features of Lung Adenocarcinomas With Programmed Death Ligand 1 Expression. Clin Lung Cancer 2017;18:e375-83.
61. Kim BT, Kim Y, Lee KS, et al. Localized form of bronchioloalveolar carcinoma: FDG PET findings. AJR Am J Roentgenol 1998;170:935-9.
62. Chun EJ, Lee HJ, Kang WJ, et al. Differentiation between malignancy and inflammation in pulmonary ground-glass nodules: The feasibility of integrated (18)F-FDG PET/CT. Lung Cancer 2009;65:180-6.
63. 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;150:514-20.
64. Song JU, Song J, Lee KJ, et al. Are There Any Additional Benefits to Performing Positron Emission Tomography/Computed Tomography Scans and Brain Magnetic Resonance Imaging on Patients with Ground-Glass Nodules Prior to Surgery? Tuberc Respir Dis (Seoul) 2017;80:368-76.
65. Yang JS, Liu YM, Mao YM, et al. Meta-analysis of CT-guided transthoracic needle biopsy for the evaluation of the ground-glass opacity pulmonary lesions. Br J Radiol 2014;87:20140276.
66. Shimizu K, Ikeda N, Tsuboi M, et al. Percutaneous CT-guided fine needle aspiration for lung cancer smaller than 2 cm and revealed by ground-glass opacity at CT. Lung Cancer 2006;51:173-9.
67. Wu CC, Maher MM, Shepard JA. Complications of CT-guided percutaneous needle biopsy of the chest: prevention and management. AJR Am J Roentgenol 2011;196:W678-82.
68. 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;284:228-43.
69. Jhun BW, Um SW, Suh GY, et al. Preoperative flexible bronchoscopy in patients with persistent ground-glass nodule. PLoS One 2015;10:e0121250.
70. Zhan P, Zhu QQ, Miu YY, et al. Comparison between endobronchial ultrasound-guided transbronchial biopsy and CT-guided transthoracic lung biopsy for the diagnosis of peripheral lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res 2017;6:23-34.
71. Han Y, Kim HJ, Kong KA, et al. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis. PLoS One 2018;13:e0191590.
72. Wang C, Li X, Zhou Z, et al. Endobronchial ultrasonography with guide sheath versus computed tomography guided transthoracic needle biopsy for peripheral pulmonary lesions: a propensity score matched analysis. J Thorac Dis 2016;8:2758-64.
73. 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:e93S-e120S.
74. Bai C, Choi CM, Chu CM, et al. Evaluation of Pulmonary Nodules: Clinical Practice Consensus Guidelines for Asia. Chest 2016;150:877-93.
75. Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax 2015;70 Suppl 2:ii1-ii54.
76. Bueno J, Landeras L, Chung JH. Updated Fleischner Society Guidelines for Managing Incidental Pulmonary Nodules: Common Questions and Challenging Scenarios. Radiographics 2018;38:1337-50.
77. NCCN Non-Small Cell Lung Cancer, National Comprehensive Cancer Network [Internet]. [cited 2022 May 9]. Available onine: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
78. Japanese Society for CT Screening. Guidelines for the management of pulmonary nodules detected by low-dose CT lung cancer screening version 3 [Internet]. Tokyo: Japanese Society for CT Screening; 2013 [cited 2022 May 9]. Available onine: http://www.jscts.org/pdf/guideline/gls3rd_english130621.pdf
79. Lung RADS, American College of Radiology [Internet]. [cited 2022 Dec 8]. Available onine: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/Lung-RADS-2022.pdf
80. NCCN Lung Cancer Screening, National Comprehensive

Cancer Network [Internet]. [cited 2022 May 9]. Available onine: https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
81. Azour L, Ko JP, Naidich DP, et al. Shades of Gray: Subsolid Nodule Considerations and Management. Chest 2021;159:2072-89.
82. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 2013;369:910-9.
83. Lui NS, Benson J, He H, et al. Sub-solid lung adenocarcinoma in Asian versus Caucasian patients: different biology but similar outcomes. J Thorac Dis 2020;12:2161-71.
84. Fogel AL, Kvedar JC. Benefits and Risks of Machine Learning Decision Support Systems. JAMA 2017;318:2356.
85. Chartrand G, Cheng PM, Vorontsov E, et al. Deep Learning: A Primer for Radiologists. Radiographics 2017;37:2113-31.
86. Ather S, Kadir T, Gleeson F. Artificial intelligence and radiomics in pulmonary nodule management: current status and future applications. Clin Radiol 2020;75:13-9.
87. Nam JG, Park S, Hwang EJ, et al. Development and Validation of Deep Learning-based Automatic Detection Algorithm for Malignant Pulmonary Nodules on Chest Radiographs. Radiology 2019;290:218-28.
88. Sim Y, Chung MJ, Kotter E, et al. Deep Convolutional Neural Network-based Software Improves Radiologist Detection of Malignant Lung Nodules on Chest Radiographs. Radiology 2020;294:199-209.
89. Wang X, Gao M, Xie J, et al. Development, Validation, and Comparison of Image-Based, Clinical Feature-Based and Fusion Artificial Intelligence Diagnostic Models in Differentiating Benign and Malignant Pulmonary Ground-Glass Nodules. Front Oncol 2022;12:892890.
90. Gong J, Liu J, Hao W, et al. A deep residual learning network for predicting lung adenocarcinoma manifesting as ground-glass nodule on CT images. Eur Radiol 2020;30:1847-55.
91. Hu X, Gong J, Zhou W, et al. Computer-aided diagnosis of ground glass pulmonary nodule by fusing deep learning and radiomics features. Phys Med Biol 2021;66:065015.
92. Yoon HJ, Choi J, Kim E, et al. Deep learning analysis to predict EGFR mutation status in lung adenocarcinoma manifesting as pure ground-glass opacity nodules on CT. Front Oncol 2022;12:951575.
93. 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;146:24-30.
94. 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;145:66-71.
95. Cho JH, Choi YS, Kim J, et al. Long-term outcomes of wedge resection for pulmonary ground-glass opacity nodules. Ann Thorac Surg 2015;99:218-22.
96. 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;106:1682-90.
97. Miyoshi T, Aokage K, Katsumata S, et al. Ground-Glass Opacity Is a Strong Prognosticator for Pathologic Stage IA Lung Adenocarcinoma. Ann Thorac Surg 2019;108:249-55.
98. 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;163:289-301.e2.
99. 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;399:1607-17.
100. Altorki NK, Wang X, Kozono D, et al. PL03.06 Lobar or Sub-lobar Resection for Peripheral Clinical Stage IA = 2 cm Non-small Cell Lung Cancer (NSCLC): Results From an International Randomized Phase III Trial (CALGB 140503 [Alliance]). J Thorac Oncol 2022;17:S1-S2.
101. Khakwani A, Harden S, Beckett P, et al. Post-treatment survival difference between lobectomy and stereotactic ablative radiotherapy in stage I non-small cell lung cancer in England. Thorax 2020;75:237-43.
102. Berry MF, Hanna J, Tong BC, et al. Risk factors for morbidity after lobectomy for lung cancer in elderly patients. Ann Thorac Surg 2009;88:1093-9.
103. Bravo Iñiguez CE, Armstrong KW, Cooper Z, et al. Thirty-Day Mortality After Lobectomy in Elderly Patients Eligible for Lung Cancer Screening. Ann Thorac Surg 2016;101:541-6.
104. Powell HA, Tata LJ, Baldwin DR, et al. Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit. Thorax 2013;68:826-34.
105. Hammer MM, Palazzo LL, Eckel AL, et al. A Decision Analysis of Follow-up and Treatment Algorithms for Nonsolid Pulmonary Nodules. Radiology 2019;290:506-13.

106. Iguchi T, Hiraki T, Gobara H, et al. Percutaneous radiofrequency ablation of lung cancer presenting as ground-glass opacity. Cardiovasc Intervent Radiol 2015;38:409-15.
107. Lencioni R, Crocetti L, Cioni R, et al. Radiofrequency ablation of lung malignancies: where do we stand? Cardiovasc Intervent Radiol 2004;27:581-90.
108. Sharma A, Abtin F, Shepard JA. Image-guided ablative therapies for lung cancer. Radiol Clin North Am 2012;50:975-99.
109. Ishiwata T, Motooka Y, Ujiie H, et al. Endobronchial ultrasound-guided bipolar radiofrequency ablation for lung cancer: A first-in-human clinical trial. J Thorac Cardiovasc Surg 2022;164:1188-1197.e2.
110. Lu W, Cham MD, Qi L, et al. The impact of chemotherapy on persistent ground-glass nodules in patients with lung adenocarcinoma. J Thorac Dis 2017;9:4743-9.
111. Kang N, Kim KH, Jeong BH, et al. The Impact of EGFR Tyrosine Kinase Inhibitor on the Natural Course of Concurrent Subsolid Nodules in Patients with Non-Small Cell Lung Cancer. Cancer Res Treat 2022;54:817-26.
112. Bonanni B, Serrano D, Maisonneuve P, et al. Low-Dose Aspirin in High-Risk Individuals With Screen-Detected Subsolid Lung Nodules: A Randomized Phase II Trial. JNCI Cancer Spectr 2020;4:pkaa096.
113. Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.
114. Chung JH, Choe G, Jheon S, et al. Epidermal growth factor receptor mutation and pathologic-radiologic correlation between multiple lung nodules with ground-glass opacity differentiates multicentric origin from intrapulmonary spread. J Thorac Oncol 2009;4:1490-5.
115. Detterbeck FC, Marom EM, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification. J Thorac Oncol 2016;11:666-80.
116. Wang X, Wu M, Shen H, et al. Comparison of Clinical and Pathological Characteristics Between Extremely Multiple GGNs and Single GGNs. Front Oncol 2021;11:725475.
117. Kim HK, Choi YS, Kim J, et al. Management of multiple pure ground-glass opacity lesions in patients with bronchioloalveolar carcinoma. J Thorac Oncol 2010;5:206-10.
118. Hattori A, Matsunaga T, Takamochi K, et al. Surgical Management of Multifocal Ground-Glass Opacities of the Lung: Correlation of Clinicopathologic and Radiologic Findings. Thorac Cardiovasc Surg 2017;65:142-9.

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