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Guidelines for the Investigation and Management of Ground Glass Nodules

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The clinical significance of ground-glass nodules (GGNs) has been investigated in extensive clinical research for many years. The natural history of GGNs is known to be closely related to their size, proportion of solid components, and size progression over time. Based on these data, several guidelines for GGN management have been published worldwide. The indications for nonsurgical biopsy or surgical resection of GGNs are as follows: pure GGNs between 5 and 10 mm in size if they increase in size or show development of a solid component at follow-up, pure GGNs >10–15 mm that remain stable but persistent, part-solid nodules >8 mm persisting at follow-up, or part-solid nodules with a solid component >6 mm at follow-up. Newly updated data considering geographical or racial factors and recent developments in surgical techniques may improve the surgical indications for GGNs in the near future.

Keywords: Ground glass nodules, Preinvasive lung cancer, Non-small cell lung cancer, Guideline, Surgery

Introduction

The importance of the early diagnosis of lung cancer was proven in the National Lung Screening Trial, which showed that low-dose computed tomography (CT) in high-risk individuals reduced the mortality rate of lung cancer [1]. Based on this trial, the US Preventive Services Task Forces and the Ministry of Health and Welfare of South Korea updated their guidelines for lung cancer screening to expand the indications for early diagnosis [2]. This increased utilization of CT has led to the discovery of large numbers of ground-glass nodules (GGNs) and solitary nodules [3].

The clinical significance of GGNs has been investigated in extensive clinical research for many years. The natural history of GGNs is known to be closely related to their size, proportion of solid components, and size progression over time [3-5]. Based on these data, several guidelines for GGN management have been provided worldwide.

However, recent advancements in technology for detecting or managing GGNs with unsolved issues may lead to guideline updates. In particular, recent developments in surgical techniques have driven amendments to these surgery-oriented guidelines to offer patients the best treatment options [3].

Japanese Society for CT Screening

The Japanese Society for CT Screening guidelines were devised from a radiology/CT perspective [6]. All patients are subjected to CT surveillance. Biopsy or surgery is reserved for lesions that are >15 mm in size and have grown since the follow-up visit or have developed a solid component >5 mm in size. Intriguingly, these guidelines allow individual hospitals to proceed to biopsy or surgery for smaller part-solid nodules even if the solid component is ≤5 mm, perhaps reflective of the greater concern over the probability of malignancy in GGNs in East Asia [7].

American College of Chest Physicians guidelines

The American College of Chest Physicians guidelines provide a slightly more multidisciplinary perspective [3,8].

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Pure GGNs ≤5 mm in size require no further evaluation, while pure GGNs >5 mm require annual surveillance with chest CT for at least 3 years.

Biopsy or surgery is performed for pure GGNs that grow or develop a solid component during follow-up. If they are pure and >10 mm in size on initial CT, early follow-up at 3 months may be indicated for nonsolid nodules >10 mm in size (followed by nonsurgical biopsy and/or surgical resection for persistent nodules).

A part-solid nodule ≤8 mm in size requires CT surveillance at approximately 3, 12, and 24 months, followed by annual CT surveillance for an additional 1–3 years. A part-solid nodule >8 mm requires repeat chest CT at 3 months, followed by further evaluation with positron emission tomography (PET), nonsurgical biopsy, and/or surgical resection if persistent. Part-solid nodules >15 mm on presentation should directly proceed to further evaluation with PET-CT, nonsurgical biopsy, and/or surgical resection.

British Thoracic Society guidelines

The British Thoracic Society guidelines provide more clarity on the use of further imaging, with ordinal scale reporting for PET-CT recommended to facilitate incorporation into risk models and more clarity on the location of the biopsy. It contains recommendations for the threshold for treatment without histological confirmation [9].

GGNs <5 mm in size that are known to have been stable for over 4 years do not require follow-up, whereas all others require repeat CT at 3 months. GGNs that persist and have morphological features that are suggestive of malignancy can be subjected to surgical excision. For GGNs that show growth or an altered morphology, surgical resection is mandatory.

Asian consensus guidelines

In 2016, the Asian consensus guidelines were developed because of the increasing incidence and distinctive characteristics observed in patients with lung cancer in Asia [10]. For the evaluation of pulmonary nodules in Asian patients, clinicians may consider data unique to Asian patients, such as exposure to air pollution, a higher smoking rate, and a high prevalence of granulomatous disease and other infectious causes of pulmonary nodules. The key differences between the Asian consensus guidelines and other guidelines are the considerations for the extended surveillance of nodules and the greater emphasis on nonsurgical biopsy instead of PET-CT due to the high prevalence of tuberculosis.

Solitary, smaller pure GGNs (<5 mm) require no follow-up surveillance CT, whereas solitary, larger pure GGNs (≥5 mm) require annual follow-up surveillance CT for at least 3 years. Clinicians should consider ongoing annual surveillance CT depending on a discussion with the patient.

Solitary, smaller part-solid nodules (<8 mm) require follow-up CT examinations at 3, 12, and 24 months and then annually thereafter. Solitary, larger part-solid nodules (≥8 mm) require initial follow-up surveillance CT at 3 months, with consideration for antimicrobial therapy. If nodules persist beyond 3 months, nonsurgical biopsy and/or surgical biopsy is recommended, and PET-CT is an additional option for the staging of the disease before surgical resection. Clinicians should consider ongoing annual surveillance CT depending on a discussion with the patient.

Fleischner Society guidelines

The Fleischner Society first published recommendations for the management of small pulmonary nodules in a statement in 2005 [11]; these recommendations were subsequently updated in 2017 to overcome important limitations, particularly the insufficiently detailed consideration of subsolid lung nodules [12].

Lesions should be established as true GGNs, preferably with the use of contiguous thin CT sections (1 mm thick). Solitary, smaller pure GGNs (<6 mm) require no follow-up surveillance CT. Solitary, larger pure GGNs (≥6 mm) require initial follow-up surveillance CT within 6–12 months to determine persistence, followed by surveillance CT every 2 years until 5 years if they remain persistent and unchanged.

Solitary, smaller part-solid nodules (<6 mm) require no follow-up surveillance CT, whereas solitary, larger part-solid nodules (≥6 mm) require initial follow-up CT within 3–6 months to determine persistence. If they remain persistent and the solid component is <6 mm in size, annual surveillance CT is performed for a minimum of 5 years. PET/CT, nonsurgical biopsy, or surgical resection is recommended for nodules with suspicious features (lobulated margins or cystic components), a developing solid component, or a large solid component (≥8 mm).

Multiple smaller subsolid nodules (<6 mm) require initial follow-up surveillance CT within 3–6 months, followed by surveillance CT at 2 and 4 years if they remain persistent and unchanged. Multiple larger subsolid nodules (≥6

Table 1. Recommendations for the management of pure GGNs and part-solid nodules

Nodule type	Work-up	Japanese Society (2012)	ACCP (2013)	BTS (2015)	Asian consensus (2016)	Fleischner Society (2017)	NCCN (2021)
Pure GGN	No further evaluation		≤5 mm	≤5 mm	≤5 mm	<6 mm	<6 mm
	F/U CT	<15 mm[a]	>5 mm[b]	>5 mm; F/U CT at 3 months, then: (1) Resolved: discharge (2) Stable: assess risk of malignancy: low-risk (F/U CT at 1, 2, 4 years), high-risk (F/U CT, nonsurgical and/or surgical resection) (3) Growth/altered morphology: resection	>5 mm[c]	≥6 mm[d]	≥6 mm[d]
	Nonsurgical biopsy or surgical resection	≥15 mm	(1) >5 mm and for nodule that solid component or growth develop on F/U CT (2) >10 mm and persistent at F/U CT[e]			≥6 mm and for nodules that have a solid component or grow/develop	≥20 mm and for nodules that grow/develop
Part-solid nodule	No further evaluation			≤5 mm		<6 mm	<6 mm
	F/U CT	<15 mm and solid component ≤5 mm[a]	≤8 mm[f]	>5 mm; F/U CT at 3 months, then: (1) Resolved: discharge (2) Stable: assess risk of malignancy: low-risk (F/U CT at 1, 2, 4 years), high-risk (F/U CT, nonsurgical and/or surgical resection) (3) Growth/altered morphology: resection	≤8 mm[g]	≥6 mm[h]	≥6 mm[h]
	Nonsurgical biopsy or surgical resection	(1) <15 mm and solid component >5 mm (2) ≥15 mm	>8 mm and persistent at F/U CT[i]		>8 mm and persistent on F/U C/T[j]	For nodules with suspicious morphology (i.e., lobulated margins or cystic components), or growing solid component, or solid component >8 mm	≥6 mm and for nodules with a solid component ≥6 mm

GGN, ground-glass nodule; ACCP, American College of Chest Physicians; BTS, British Thoracic Society; NCCN, National Comprehensive Cancer Network; F/U, follow-up; CT, computed tomography; PET, positron emission tomography.
[a]F/U CT examinations at 3,12, and 24 months, and then: (1) size increase or solid component >5 mm: nonsurgical and/or surgical resection; (2) stable: F/U CT examinations should be continued. [b]F/U CT examinations annually for 3 years. [c]Annual F/U CT examinations for 3 years, and then consider ongoing annual surveillance CT examinations depending on clinical judgment and patient preference. [d]F/U CT examination at 6–12 months, and then every 2 years for 5 years. [e]If the nodule size is >10 mm, a F/U CT examination at 3 months may be indicated. Nonsurgical biopsy and/or surgical resection is needed for nodules that persist on the F/U CT examination. [f]F/U CT examinations at 3, 12, and 24 months, and then annually for 1–3 years. [g]F/U CT examinations at 3, 12, and 24 months, and then annually. Consider ongoing annual surveillance CT examinations depending on clinical judgment and patient preference. [h]F/U CT examination at 3–6 months, and then annually for 5 years. [i]If the nodule size >8 mm, F/U CT examination at 3 months. PET, nonsurgical biopsy, and/or surgical resection is needed for nodules that persist on the F/U CT examination. [j]Empirical antimicrobial therapy can be considered, and PET is an additional option for staging of disease before surgical resection.

mm) also require initial follow-up surveillance CT within 3–6 months, and the most suspicious nodule will determine subsequent management.

National Comprehensive Cancer Network guidelines

The National Comprehensive Cancer Network guidelines, which are drafted by an intentionally multidisciplinary panel, are possibly the most widely used and referenced [13]. Solitary smaller pure GGNs and part-sloid nodules (<6 mm) require no follow-up surveillance CT, whereas solitary larger pure GGNs (≥6 mm) require an initial follow-up surveillance CT within 6–12 months, followed by surveillance CT every 2 years until 5 years. Solitary larger part-solid nodules (≥6 mm) require follow-up surveillance CT within 3–6 months. PET-CT, biopsy, or surgical resection is considered for nodules with a solid component ≥6 mm in size.

Lung Imaging Reporting and Data System

The Lung Imaging Reporting and Data System (Lung-RADS) is not a guideline, but a standardized reporting tool. In 2014, the American College of Radiology developed Lung-RADS ver. 1.0 (American College of Radiology, Reston, VA, USA) to standardize lung cancer screening CT reporting, and management recommendations [14]. Lung-RADS ver. 1.0 (American College of Radiology) was modified and adopted for the national lung cancer screening program in Korea. After the system was revised, Lung-RADS ver. 1.1 (American College of Radiology) was published in 2019 [15].

The Lung-RADS scoring system is classified into categories 1–4 according to the nodule consistency (solid, part-solid, and ground-glass), size, and growth (increase in nodule size >1.5 mm). Lung-RADS category 4 is further divided into 3 subcategories (4-A, 4-B, and 4-X) according to the nature of the nodule. As a modifier, the letter "S" is added to categories 0–4 coding (e.g., 4AS, 4BS) to describe any clinically significant incidental findings.

Pure GGNs (≥30 mm) are classified into category 3 (probably benign) and part-solid nodules (≥6 mm) with a solid component ≥6 mm in size are classified into category 4 (suspicious).

Conclusion

The guidelines for GGNs are inconsistent and still require updating as data continue to be gathered on the natural history of GGNs. The current guidelines for pure GGNs and part-solid nodules are summarized in Table 1.

Based on the present information provided, the indications for nonsurgical biopsy or the surgical resection of GGNs are as follows: pure GGNs between 5 and 10 mm in size if they increase in size or develop a solid component at follow-up, pure GGNs >10–15 mm that remain stable but persistent, part-solid nodules >8 mm persisting at follow-up, or part-solid nodules with a solid component >6 mm at follow-up. Newly updated data considering geographical or racial factors and recent developments in surgical techniques may improve the surgical indications for GGNs in the near future.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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