Guidelines for the Management of Pulmonary Nodules Detected by Low-dose CT Lung Cancer Screening

1. Introduction

In January 2005, the Committee for Preparation of Clinical Practice Guidelines for the Management of CT-screening-detected Pulmonary Nodules of the Japanese Society of CT Screening published the "Guidelines for Pulmonary Nodule Management, Version 1", which had been prepared for screening CT images that had been reconstructed at 10 mm intervals, on the homepage of the Japanese Society of CT Screening. In April 2009, the Committee drafted revised guidelines based on subsequent cases of lung cancer detected by multislice CT, and the Committee published them on the homepage as the "Guidelines for Pulmonary Nodules Management, Version 2". The key points of the revisions were: 1) in principle, the size criterion for workup of a pure GGO (ground-glass opacity)[1)] was changed to 15 mm or more, 2) it was recommended that a mixed GGO[1)] be rescanned by thin-section CT (TS-CT) 3 months later to exclude an inflammatory lesion], 3) the recommendation that TS-CT scanning of solid nodules be performed 18 months later was deleted.

However, because multislice CT has subsequently become more widely adopted, we have drafted and published the current guidelines, "Guidelines for Pulmonary Nodules Management, Version 3" (Fig. 1). The key points of the revisions are: 1) size is now judged on the basis of the value obtained by calculating the average of the maximal diameter and the perpendicular diameter, instead of on the basis of the maximal diameter alone, 2) the recommendations for follow-up examinations for solid nodules now depend on whether the patient is a smoker or non-smoker, 3) after the release of a new international classification of adenocarcinoma of the lung in February 2011[2)] that classifies adenocarcinoma of the lung into adenocarcinoma in situ (AIS), which is non-invasive, minimally invasive adenocarcinoma (MIA), in which the size of the invasive focus is 5 mm or less, and invasive adenocarcinoma, in which the size of the invasive focus is greater than 5 mm, etc., we lumped pure GGOs (or ground-glass nodules, GGNs) and mixed GGOs (or part-solid nodules) into a single category and in the present Guidelines propose a decision tree based on the size of the pulmonary nodule (≥15 mm or <15 mm) and the size of its internal solid component (≤5 mm or >5 mm), and 4) the present Guidelines propose a more detailed follow-up examination of pulmonary nodules that have been newly detected by repeat CT screening (Fig. 1).

The Fleischner Society guidelines list a PET examination as one of the choices of diagnostic imaging methods that can be used to diagnose solid nodules measuring 8 mm or more[3)]. The NELSON study reported the usefulness of volume doubling time (VDT) calculated on a workstation for decision tree of pulmonary nodules[4)]. The Danish Lung Cancer Screening Trial reported finding that a combination of VDT and a PET examination was useful for differentiating between benign and malignant pulmonary nodules[5)]. However, we have not introduced VDT measurements on a workstation or PET examinations into the decision tree in our Guidelines, because it is not easy to perform VDT measurements on workstations or PET studies in ordinary clinical settings in Japan.

Furthermore, "low-dose imaging" has become a global challenge not only for CT lung cancer screening but in ordinary clinical settings. CT screening for lung cancer is still the subject of research, and it will be essential to construct a system that is capable of constantly collecting data from each of the CT lung cancer screening projects that are under way.

2. Guidelines for Pulmonary Nodule Management, Version 3

A pulmonary nodule is appears as a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter[6]. Based on its consistency on TS-CT images pulmonary nodules are classified as a homogeneous ground-glass opacity (pure GGO), a ground-glass opacity part of which contains a soft-tissue attenuation (mixed GGO), or an opacity that exhibits soft-tissue attenuation (a solid nodule). The Fleischner Society glossary classifies pulmonary nodules into ground-glass nodules (nonsolid nodules), part-solid nodules (semisolid nodules), and solid nodules[6]. GGNs are recognizable as hazy increases in attenuation in a lung field that do not obliterate the bronchial and vascular margins[6]. Since the terms "pure ground-glass nodule (GGN)" and "part-solid nodule" are used in the new international classification of pulmonary adenocarcinoma[2], Version 3 of the Guidelines uses the term "pure GGN" for "pure GGO" and the term "part-solid nodule" for "mixed" GGO. Nodules in which calcification is visible on TS-CT scans are thought to represent old pulmonary tuberculosis lesions and are excluded from the recommendations in the Guidelines for subsequent follow-up examinations.

A. Role of the screening sites

The scanning and imaging reconstruction protocols for lung cancer screening by multislice CT at each of the screening sites are shown in Table 1, and depending on the CT scanner, an automatic dose-modulating function (RealEC, AutoMA, etc.) can be used. As shown in Table 1, CTDI (computed tomography dose index) volumes for the screening examinations range from 1.32 mGy to 3.1 mGy. CT images having a slice thickness ≤5 mm and reconstruction interval ≤5 mm are recommended. The size criterion for performing TS-CT scans for pulmonary nodules detected on screening CT scans is a 5-mm or larger value for the average of the maximal diameter and perpendicular diameter of the nodule. If the size of a pulmonary nodule is less than 5 mm, a CT screening examination 12 months later is recommended. The fact that pulmonary nodules having a maximal diameter ≥4 mm were considered to be positive in the NLST (National Lung Screening Trial)[8] appears to be one of the reasons why there were many false positives. The Fleischner Society guidelines for managing solid nodules also use a cutoff value for size that is the average of the length and width of the nodule[3]. A cutoff value that is the average value of the length and width of the nodule is also used in the I-ELCAP (International Early Lung Cancer Action Program) [9], and in that program a workup is conducted when the size of a solid nodule or a part-solid nodule is 5 mm or larger.

B. Role of hospitals where workups are performed

If the slice thickness of the CT images provided by the screening site is greater than 3 mm, the first TS-CT should be performed one month later, and any pulmonary nodules ≥5 mm that are detected on the first TS-CT images are classified into solid, part-solid, or pure GGN according to their consistency. Even when scanning is performed by low-dose multislice CT, if the slice thickness is no greater than 3 mm and the reconstruction interval is no greater than 3 mm, any pulmonary nodules ≥5 mm that are detected can be classified as a solid, part-solid, or pure GGN, based on their consistency. If a screening site provides the screening CT images to a hospital, the first TS-CT examination one month later at the hospital can be omitted, and it is advisable to perform the first TS-CT examination 3 months after the nodule was detected.

a) Solid nodules

In principle, a workup is performed when a solid nodule measures ≥10 mm on a TS-CT scan. When the size of a solid nodule on a TS-CT scan is in the 5 mm to less than 10 mm range and the patient is a smoker, a follow-up examination by TS-CT is performed after 3 months, 6 months, 12 months, 18 months, and 24 months, whereas if the patient is a nonsmoker, a follow-up examination by TS-CT is performed after 4 months, 12 months, and 24 months. The reason for establishing different intervals between the follow-up examinations for smokers and nonsmokers is that the lung-cancer tumor doubling time is shorter in smokers[10]. Regardless of whether the patient is a smoker or a nonsmoker, i) if the nodule increases in size, a workup is performed, ii) if there is no change within 2 years, follow-up examinations by TS-CT are discontinued, and iii) if the nodule decreases in size or disappears, a return is made to screening CT at the screening site. If an intrapulmonary lymph node is strongly suspected based on the TS-CT findings, a follow-up examination by TS-CT is performed 3 months later regardless of the size of the nodule. If there is no change in size, follow-up examinations are performed until 12 months later. Intrapulmonary lymph nodes are present just beneath the pleura of the middle lobe or lower lobe or are in contact with the interlobar fissure. They often appear polygonal on TS-CT images because of contact with the interlobular septa, and when they are present just beneath the pleura, a linear structure that consists of the interlobular septum is sometimes seen between the nodule and the pleura.

b) Part-solid nodules

Because of the high probability of part-solid nodules being malignant, Version 1 of the Guidelines recommended an immediate workup for part-solid nodules irrespective of size. However, a workup should be performed 3 months later in order to exclude inflammatory lesion presenting as a part-solid nodule. A portion of the decision tree was revised based on the new international classification of pulmonary adenocarcinoma. If the overall size of a part-solid nodule (GGO component) is 15 mm or more, a workup is performed. If it is less than 15 mm in size, a workup is performed if the size of the solid component is greater than 5 mm, but if the size of the solid component is no more than 5 mm, follow-up CT can be performed instead. Of course, the size of the invasive focus in the pathology specimen and the solid component on the CT image are not the same. Sone et al. defined a component with a CT value of -350 HU or more as a "tumor core," and if its size was greater than 15 mm and the CT value was greater than -70 HU, they reported that the pathological stage was higher than IA and that there was a high risk of postoperative recurrence[13].

c) Pure GGNs

If a pure GGN is 15 mm or larger in size on a TS-CT scan, a workup should be performed to make a definitive diagnosis. If a pure GGN is less than 15 mm in size, a portion of the decision tree was altered based on the new international classification of pulmonary adenocarcinoma. A follow-up TS-CT is performed after 3 months, 12 months, and 24 months, and i) if the size or attenuation of the nodule has increased, a workup is performed, ii) even if a solid component has developed, if it is less than 5 mm in size, further follow-up CT can be performed, and iii) even if there is no change after 24 months, in principle, follow-up CT examinations should be continued at the hospital.

d) New nodules

When a new nodule is detected during annual screening examinations (Fig. 1 includes a decision tree for new nodules discovered during the course of follow-up, not just nodules discovered during the baseline screening), if it is a solid nodule ≥10 mm, a workup is performed. If it is less than 10 mm in size and the patient is a smoker, a follow-up TS-CT examination is performed at 1 month, 3 months, 6 months, and 12 months, whereas if the

patient is a nonsmoker, a follow-up TS-CT examination is performed at 1 month, 4 months, and 12 months. Regardless of whether the patient is a smoker or nonsmoker, if there has been no change in size after 12 months, the patient returns to the screening site, and the patient's course is monitored by annual screening examinations. If a part-solid or pure GGN has not disappeared or decreased in size 4 months later, and if the solid component has not increased in size, a follow-up examination is performed 12 months later. If there is still no change after 12 months, in principle, a follow-up CT at a hospital is necessary every year thereafter.

e) Follow-up CT

Because it is necessary to confirm that no new lesions have developed in other areas of the lung, CT of the entire lung should be performed during the follow-up CT examinations, not just TS-CT of the targeted nodule. Since the resolution of the multislice CT images is better in the direction of the body axis, TS-CT images can be reconstructed from the raw data obtained by scanning the whole lung. When performing follow-up examinations by multislice CT, it is advisable to perform them at a low dose within the area where follow-up CT of the pulmonary nodule is possible. A simulation study reported that follow-up examinations by 10 mAs CT scans is possible for following up pulmonary nodules detected by CT screening[14], and image quality has been reported to enable diagnosis of pulmonary nodules even in actual screening examinations performed with 1-mm slice thickness images at 15 mAs (not yet published).

3. Conclusion

The evidence for some of the above is insufficient. In the near future it will be necessary to modify the above guidelines to make them more appropriate based on the results of follow-up CT examinations of large numbers of lung cancer patients whose lesions have been detected by CT screening examinations. In order to establish robust guidelines, collecting screening examination data at each screening site, including examinee's information (smoking, family history, etc.), information about the lung cancer that was discovered (histological type, size, stage, CT images, etc.), and other information, is an urgent task.

Table 1. Examples of Scanning and Reconstruction Protocols of Multislice CT

Screening Site	A	B	C	D
Number of Detectors	64	64	16	64
kVp	120	120	120	120
mA	50	auto mA (10-60)	50	30
Second/ratation	0.5	0.4	0.75	0.5
mAs				15
Pitch Factor	0.985	1.375	1,438	0.98
Collimation	0.625mm×64	0.625mm×64	1mm×16	1X32
Reconstruction	5mm	2.5mm	3mm	5mm
	2mm	0.625mm		1mm
Lung Field（WW/WL）	1500/-500	1600/-600	1600/-600	2000/-750
Mdeiastinal Field （WW/WL）		350/0-20	400/35	
CTDIvol mGy	1.9	1.32	3.1	2.2
DLP mGycm	71.5	46.69	119.7	88.7

Table 2. Examples of Exposure Dose

	Single slice CT			Multislice CT		
	Standard	Low-dose	Thin-section CT	Standard	Low-dose	Thin-section CT
Tube Voltage (kVp)	120	120	120	120	120	120
Tube Current (mA)	150	50	400	200	30	300
second/rotation	1	1	0.75	0.5	0.5	0.5
mAs	150	50	300	100	15	150
Collimation	10	10	2	1×16	1×16	0.5×16
Helical Pitch	1	2	1	0.94	0.94	0.69
Scanning Range	¶	¶	4 cm	¶	¶	4 cm
Exposure Dose (mSv)	5.7	0.97	2.1	7.1	1.1	3.7

¶ apex to diaphragm

The results calculated by using a computer software program specifically designed to estimate exposure doses[15] are shown in Table 2. It should be noted that the exposure dose in Table 2 is a reference value for screenees. CT lung cancer screening should be performed at the lowest dose settings possible, because the screenees are asymptomatic. The minimum exposure dose during a CT lung cancer screening examination with a multislice CT scanner is 0.43 mSv.

References

1.Nakata M, Saeki H, Takata I, et al. Focal ground-glass opacity detected by low-dose helical CT. Chest,2002;121:1464:1467.
2.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 Thrac Oncol. 2011; 6:244-285.
3.MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005; 237:395-400.
4.van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361:2221-2229.
5.Ashraf H, Dirksen A, Loft A, et al. Combined use of positron emission tomography and volume doubling time in lung cancer screening with low-dose CT screening. Thorax 2011; 66:3151-3159.
6.Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology,2008;246:697-722.
7.Sone S, Nakayama T, Honda T,et al. CT findings of early-stage small cell lung cancer in a low-dose CT screening programme. Lung Cancer, 2007;56:207-215.
8.National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study desing. Radiology 2011;258:243-253.
9.Henschke CI, Yip R, Simith JP, et al. CT screening for lung cancer: update of the definition of positive result. J Thorac Oncol 2011;6:5517(Supplement).
10.Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. Brit J Radiol 2000;73:1252-1259.
11.Li F, Sone S, Abe H, et al. Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. Radiology,2004; 233:793-798.
12.Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053-1057.
13.Sone S, Hanaoka T, Ogata H,et al. Small peripheral lung carcinomas with five-year post-surgical follow-up: assessment by semi-atutomated volumetric measurement of tumour size, CT value and growth rate on TSCT. Eur Radiol 2012;22:104-119.
14.Christe A, Torrente JC, Lin M, et al. CT screening and follow-up of lung nodules: effects of tube current-time setting and nodule size and density on detectability and tube current-time setting on apparent size. AJR 2011; 197:623-630.
15.Jones DG, Shrimpton PC. Normalized organ doses for x-ray CT calculated using Monte Carlo techniques. NRPB-SR250. Chilton, England: National Radiological Protection Board,1993.

Sample Images

A case of solid nodule

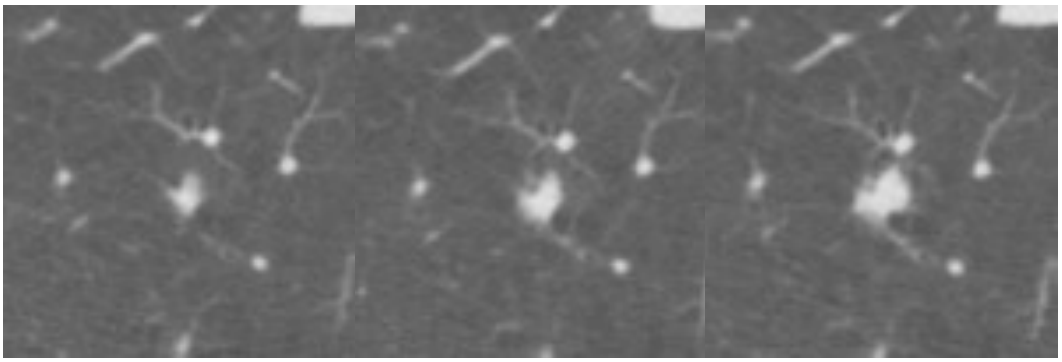

Figure A. Axial CT images acquired during low-dose multislice CT lung cancer screening in which scanning conditions were 15 mAs, and 2 mm X 4 rows and the CT images were reconstructed at 1-mm intervals, and a 2-mm slice thickness. The CT image on the left was acquired during the baseline screening. The CT images in the center and on the right were taken 6 months later and 12 months later, respectively. The pathological diagnosis of the tumor was adenocarcinoma (Noguchi's Type E), and the pathological stage was IA. The size of tumor measured in the pathological specimen was 16 mm.

A case of part-solid nodule

Minimally invasive adenocarcinoma

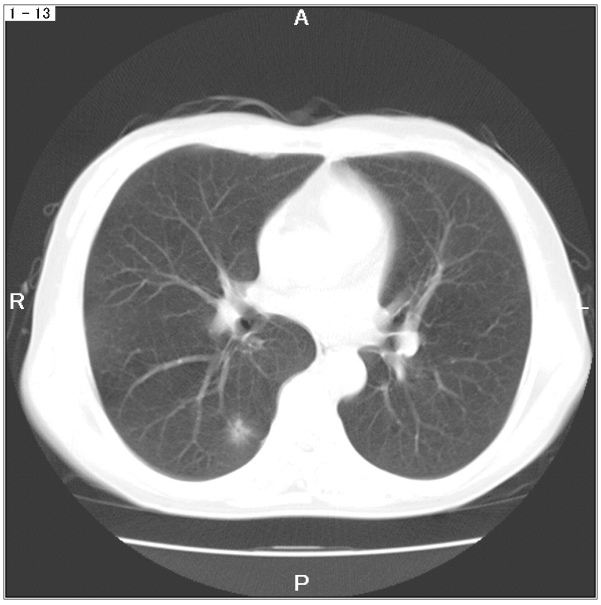

Figure B. Screening CT

Figure C. Thin-section CT shows a part-solid nodule in segment 6 of the right lower lobe.

A case of pure GGN

Adenocarcinoma in situ

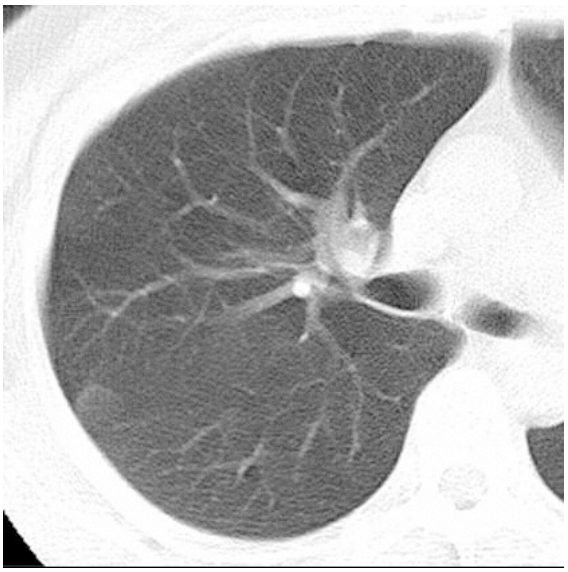

Figure D. Screening CT

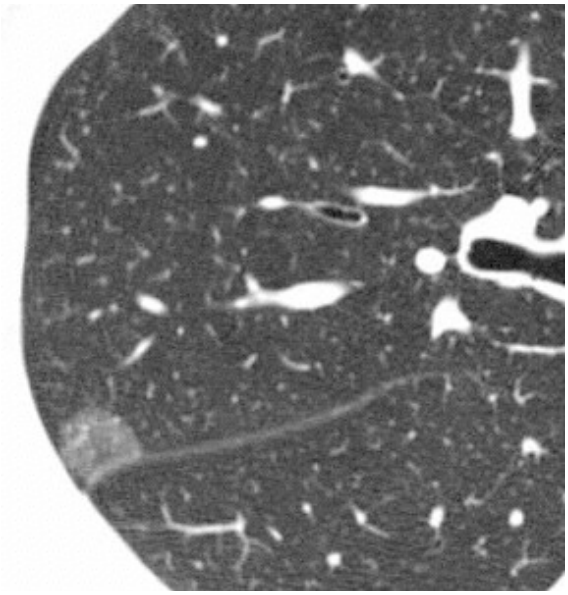

Figure E. Thin-section CT shows a pure GGN in segment 2 of the right upper lobe.

A case of solid nodule

Figure F. Thin-section CT image acquired under scanning conditions of 150 mAs, and 0.5 mm X 16 rows, and reconstructed at 1-mm intervals and a 1-mm slice thickness. A solid nodule is located in segment 8 of the left lower lobe. The nodule is polygonal in shape, and a linear shadow is visible between the nodule and the pleura. This solid nodule is thought to be an intrapulmonary lymph node.