

# Guidelines for the Management of Pulmonary Nodules Detected by Low-dose CT Lung Cancer Screening Version 3

## 1. Introduction

In January 2005, the Pulmonary Nodules Management Committee 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 website 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 website 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)<sup>1</sup> was changed to 15 mm or more, 2) it was recommended that a mixed GGO<sup>1</sup> be rescanned by diagnostic 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) nodule size on screening CT image is now judged on the basis of the value obtained by calculating the average of the maximal diameter and the perpendicular diameter, 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 2012<sup>2</sup> that classifies adenocarcinoma of the lung into adenocarcinoma in situ (AIS), which is non-invasive, minimally invasive adenocarcinoma (MIA), in which the maximal diameter of the invasive focus is 5 mm or less, and invasive adenocarcinoma, in which the maximal diameter 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 maximal diameter of the pulmonary nodule ( $\geq 15$  mm or  $< 15$  mm) and the maximal diameter of its internal solid component ( $\leq 5$  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<sup>3</sup>. The NELSON study reported the usefulness of volume doubling time (VDT) calculated on a workstation for decision tree of pulmonary nodules<sup>4</sup>. 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<sup>5</sup>. 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 appears as a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in maximal diameter<sup>6</sup>). 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<sup>6</sup>). GGNs are recognizable as hazy increases in attenuation in a lung field that do not obliterate the bronchial and vascular margins<sup>6</sup>). Since the terms “pure ground-glass nodule (GGN)” and “part-solid nodule” are used in the new international classification of pulmonary adenocarcinoma<sup>2</sup>), 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  $\leq 5$  mm and reconstruction interval  $\leq 5$  mm are recommended. The size criterion for performing diagnostic 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  $\geq 4$  mm were considered to be positive in the NLST (National Lung Screening Trial)<sup>8</sup>) 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<sup>3</sup>). 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) <sup>9</sup>), 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 diagnostic TS-CT should be performed one month later, and any pulmonary nodules  $\geq 5$  mm that are detected on the first diagnostic TS-CT images should be classified into solid, part-solid, or pure GGN according to their consistency. Even when scanning is performed using 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 with an average maximal diameter and perpendicular diameter  $\geq 5$  mm detected during a screening CT scan should 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 diagnostic TS-CT examination performed one month later at the hospital can be omitted,

and it is advisable to perform the first diagnostic TS-CT examination 3 months after the nodule was first detected.

#### a) Solid nodules

In principle, a workup is performed when a solid nodule measures  $\geq 10$  mm in maximal diameter on a diagnostic TS-CT scan. When the maximal diameter of a solid nodule on a diagnostic 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 diagnostic 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<sup>10</sup>). 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 diagnostic 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 diagnostic TS-CT findings, a follow-up examination by diagnostic 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 diagnostic 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 their size. However, a workup should be performed 3 months later so as to exclude inflammatory lesions presenting as part-solid nodules. A portion of the decision tree was revised based on the new international classification for pulmonary adenocarcinoma. If the maximal diameter of a part-solid nodule (GGO component) is 15 mm or more, a workup is performed. If the maximal diameter is less than 15 mm in size, a workup is performed if the maximal diameter of the solid component is greater than 5 mm; if the maximal diameter of the solid component is no more than 5 mm, however, a follow-up CT examination can instead be performed. The solid component should be measured in the lung field windows. Of course, the maximal diameter of the invasive focus in the pathology specimen and the solid component on the CT image are not the same. An option exists to proceed to a workup if the size of the solid component is  $\leq 5$  mm, based on each hospital's decision tree.

#### c) Pure GGNs

If a pure GGN is 15 mm or larger in maximal diameter on a diagnostic TS-CT scan, a workup should be performed to make a definitive diagnosis. If a pure GGN is less than 15 mm in maximal diameter, 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 maximal diameter, 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  $\geq 10$  mm in maximal diameter on diagnostic TS-CT, a workup is performed. If it is less than 10 mm in maximal diameter 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<sup>14</sup>), 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.

Copyright © 2013 by The Japanese Society of CT Screening

The teaching file of CT-screening-detected adenocarcinomas based on the new international classification of adenocarcinoma of the lung is available at the following website; <http://cir.ncc.go.jp/jp/jmct3.html>.

The Pulmonary Nodules Management Committee of the Japanese Society of CT Screening

Ryutaro Kakinuma, MD, PhD<sup>1</sup>

Kazuto Ashizawa, MD, PhD<sup>2</sup>

Yoko Kusunoki, MD<sup>3</sup>

Takeshi Kobayashi, MD<sup>4</sup>

Tetsuro Kondo, MD<sup>5</sup>

Tohru Nakagawa, MD<sup>6</sup>

Masayuki Hatakeyama, MD<sup>7</sup>

Yuichiro Maruyama, MD<sup>8</sup>

Affiliations:

1. National Cancer Center Research Center for Cancer Prevention and Screening, Tokyo, Japan
2. Department of Clinical Oncology, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan
3. Hanwa Intelligent Medical Center, Sakai, Japan
4. Ishikawa Prefectural Central Hospital, Kanazawa, Japan
5. Kanagawa Cancer Center, Yokohama, Japan
6. Hitachi Health Care Center, Hitachi, Japan
7. Tokyo Anti-Tuberculosis Association, Tokyo, Japan
8. Komoro Kousei General Hospital, Komoro, Japan