The disparity between the ability of the method to detect malignant and benign nodules is substantial. Despite the argument that it could be advantageous for an automated nodule detection method to detect as many nodules (both malignant and benign) as possible while leaving the diagnostic task to the radiologist (with the eventual assistance of another automated method for nodule classification), an automated nodule detection method that preferentially detects malignant nodules is expected to provide additional clinical benefits. As may be observed from Figure 1, the effective diameters of malignant nodules tended to be larger than the effective diameters of benign nodules (a t test for difference in means between the two distributions of effective diameters yielded a significant difference with $P < 0.01$); accordingly, the effect on method performance of nodule size versus the radiologic characteristics specific to malignant nodules remains for further investigation.

It is worth noting that the overall performance of the automated detection method applied to low-dose CT scans is consistent with the overall performance of the detection method applied to a database of diagnostic CT scans (71% sensitivity with 1.5 false-positives per section) reported earlier (24). Although the rule-based and linear discriminant classifiers were established separately for the diagnostic and low-dose databases, the consistent levels of performance demonstrate robustness of the general methodology.

As expected, the overall performance of the automated lung nodule detection method decreased for nodules of increased subtlety and for nodules with an increased nonsolid component. The clinical utility of automated nodule detection methods, of course, will depend on the ability of such methods to detect those nodules most likely to be overlooked or misinterpreted by radiologists. The goal of ongoing research is to reduce the number of false-positive detections, which at present limit the clinical utility of the method, and to reduce the variability of the method across different nodule categories.

CONCLUSION

We have developed an automated lung nodule detection method that we evaluated with a large number of low-dose CT scans from a lung cancer screening program. This evaluation used a jackknife paradigm for the training and testing of the automated classifiers that distinguished nodule candidates that corresponded to actual nodules from those that corresponded to non-nodules. Because nodules demonstrate a spectrum of radiologic appearances, the performance of the automated method was evaluated on the basis of nodule malignancy status, size, subtlety, and radiographic opacity. The category-based performance analysis we present serves to underscore the importance of a full characterization of the lung nodules used by investigators when reporting results of CAD methods. Such computerized lung nodule detection methods are expected to become important parts of CT-based lung cancer screening programs (44).

ACKNOWLEDGMENTS

The authors would like to thank Maryellen L. Giger, PhD, for insightful discussions and Roger Engelmann, MS, for development of the interface used to identify the location of actual nodules and for development of the relational database used to organize the CT images. S. G. Armato, H. MacMahon, and K. Doi are shareholders in R2 Technology, Inc. (Sunnyvale, CA). K. Doi is a shareholder in Deus Technologies, Inc. (Rockville, MD).

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Published online
10.1148/radiol.2372041555
Radiology 2005; 237:684–690

Abbreviations:
A_z = area under ROC curve
CAD = computer-aided detection
GGO = ground-glass opacity
LROC = localization ROC
ROC = receiver operating characteristic

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See Materials and Methods for pertinent disclosures.

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Computer-aided Detection of Peripheral Lung Cancers Missed at CT: ROC Analyses without and with Localization[1]

PURPOSE: To retrospectively evaluate whether a difference-image computer-aided detection (CAD) scheme can help radiologists detect peripheral lung cancers missed at low-dose computed tomography (CT).

MATERIALS AND METHODS: Institutional review board approval and informed patient and observer consent were obtained. Seventeen patients (eight men and nine women; mean age, 60 years) with a missed peripheral lung cancer and 10 control subjects (five men and five women; mean age, 63 years) without cancer at low-dose CT were included in an observer study. Fourteen radiologists were divided into two groups on the basis of different image display formats: Six radiologists (group 1) reviewed CT scans with a multiformat display, and eight radiologists (group 2) reviewed images with a "stacked" cine-mode display. The radiologists, first without and then with the CAD scheme, indicated their confidence level regarding the presence (or absence) of cancer and the most likely position of a lesion on each CT scan. Receiver operating characteristic (ROC) curves were calculated without and with localization to evaluate the observers' performance.

RESULTS: With the CAD scheme, the average area under the ROC curve improved from 0.763 to 0.854 for all radiologists ($P = .002$), from 0.757 to 0.862 for group 1 ($P = .04$), and from 0.768 to 0.848 for group 2 ($P = .01$). The average sensitivity in the detection of 17 cancers improved from 52% (124 of 238 observations) to 68% (163 of 238 observations) for all radiologists ($P < .001$), from 49% (50 of 102 observations) to 71% (72 of 102 observations) for group 1 ($P = .02$), and from 54% (74 of 136 observations) to 67% (91 of 136 observations) for group 2 ($P = .006$). The localization ROC curve also improved.

CONCLUSION: Lung cancers missed at low-dose CT were very difficult to detect, even in an observer study. The use of CAD, however, can improve radiologists' performance in the detection of these subtle cancers.

In the past decade, low-dose single–detector row computed tomography (CT) with 10-mm-thick sections has been used to screen asymptomatic smoking and nonsmoking populations for lung cancer (1–3). The results of these CT screening studies showed that early peripheral lung cancers usually appeared as solitary noncalcified lesions with or without areas of ground-glass opacity (GGO), and the detection of these lesions at an early stage was greatly improved with use of low-dose CT rather than chest radiography. Most CT scans obtained in screening programs, however, showed only minor benign abnormalities, including noncancerous abnormalities such as diffuse lung disease (emphysema and interstitial changes) and focal lung disease (active infections, scars, and calcified nodules); in addition, 5%–27% of patients had noncalcified nodules that were detected at baseline screening with use of low-dose CT and 10-mm-thick sections (1–3). When reading images obtained in a CT screening program, radiologists must search for suspicious

noncalcified lung nodules, differentiate these lesions from benign nodules and lung cancer, and, finally, recommend follow-up actions for the detected lesions. In the studies mentioned above, no additional clinical information was provided to radiologists reviewing the CT scans except for age, sex, and smoking status.

At baseline CT screening performed in a general population that included smokers and nonsmokers in Nagano, Japan(2), the fraction of lung cancers among the detected noncalcified lesions was 9% and the prevalence of cancers was only 0.48%. The corresponding data were 12% and 2.7%, respectively, for smokers in the U.S. Early Lung Cancer Action Project (3). In CT screening programs, however, 32%–39% of lung cancers (4,5) were missed in previous years, and the numbers of these missed cancers were not included in the determination of the prevalence of lung cancers in these studies. We previously reported (5) that 32 missed lung cancers were very difficult to detect in the Nagano series; in general, they were very subtle and appeared as small, faint nodules with GGO that overlapped normal structures or as opacities in a complex background of other diseases.

When an automated lung nodule–detection method (6) was used, 84% of these missed lung cancers in the Nagano series were marked by the computer; however, the false-positive rate was high (1.0 false-positive marks per section, 28 false-positive marks per study), and this is not acceptable to radiologists. Recently, we developed a computer-aided detection (CAD) scheme (7) that is based on a difference-image technique for enhancing lung cancers and suppressing most normal background structures, and the false-positive rate has improved to about 3.0 marks per study (sensitivity, 87%) with use of a multiple massive training artificial neural network (8). Thus, the purpose of our study was to retrospectively evaluate whether a difference-image CAD scheme can help radiologists detect peripheral lung cancers missed at low-dose CT.

MATERIALS AND METHODS

H.M. and K.D. are shareholders in R2 Technology, Sunnyvale, Calif. K.D. is a shareholder in Deus Technology, Rockville, Md. CAD technologies developed in the Kurt Rossmann Laboratories have been licensed to companies including R2 Technology, Deus Technologies, Riverain Medical Group, Mitsubishi Space Software, Median Technologies, GE, and Toshiba.

Database

An annual low-dose CT screening program for lung cancer in Nagano, Japan, began in May 1996 and ended in March 1999. In the program, 17 892 examinations were performed in 7847 individuals (4288 men, 3559 women; mean age, 61 years; age range, 19–92 years). All individuals gave informed consent to undergo CT screening and for use of the data for research purposes. The database used in this study consisted of data from 38 low-dose CT examinations performed in 31 patients with missed peripheral lung cancers. All of the CT studies had been performed as part of the 3-year lung cancer screening program (5,6). Twenty-three cancers were missed because of detection errors, and 15 cancers were missed because of interpretation errors.

As described previously (5), the locations of missed lung cancers on sections obtained at 39 CT examinations (one examination was excluded from this study because of technical error) were determined in consensus by two radiologists (F.L. and S.S., with 20 and 42 years of experience, respectively). One radiologist (F.L.) measured the length and width of cancers on at least one section. Three radiologists (F.L., H.A., and H.M., with 20, 18, and 29 years of experience, respectively) first independently classified the low-dose CT scans with the 38 cancers into three patterns, and the final judgment was based on agreement by at least two radiologists. The mean diameter of the 38 lesions missed at low-dose CT was 12 mm (range, 6–26 mm). The following patterns were noted: 10 nodules had pure GGO (nonsolid), 16 had mixed GGO (part solid), and 12 had solid opacity.

The 31 missed cancers, which included 28 adenocarcinomas, two small cell carcinomas, and one squamous cell carcinoma, were confirmed with surgery. The CT examinations were performed with a mobile scanner (CT-W950SR; Hitachi Medical, Tokyo, Japan) with use of a low-dose protocol and a tube current of 25 or 50 mA, a scanning time of 2 seconds per rotation of the x-ray tube (tube rotation time, 2 seconds), a table speed of 10 mm/sec (pitch, 2), 10-mm collimation, and a 10-mm reconstruction interval. The mean number of sections per study was 30, and the pixel size was 0.586 or 0.684 mm for scans with a 512 × 512 image matrix size. The use of this database and the participation of radiologists in this observer performance study were approved by the University of Chicago Institutional Review Board. Informed consent for the observer performance study was obtained from all observers.

CAD Scheme

Our scheme was based on a difference-image technique (7,9,10) that enhances the lung nodules and suppresses most of the background normal structures. The difference image for each CT study was obtained by subtracting the nodule-suppressed image processed with a ring average filter from the nodule-enhanced image processed with a matched filter. By applying a multiple-gray-level threshold technique to the difference image, on which most nodules showed strong enhancement, the initial nodule candidates were identified. A number of false-positive findings were removed by using the two rule-based schemes on the localized image features related to morphologic characteristics and gray levels, and a false-positive rate of 15.8 per study was achieved (7). Most (81%) of the remaining false-positive findings were eliminated without removing any true-positive findings by using a multiple massive training artificial neural network trained to reduce various types of false-positive findings (8). The CAD scheme had a sensitivity of 87% (33 of 38 cancers) for 38 missed cancers, with an average of 3.0 false-positive findings per study (7,8).

Observer Study

Among 23 studies in which cancer was missed due to detection errors, 17 studies in 17 patients (eight men and nine women; mean age, 60 years; age range, 48–69 years) were performed the year before the cancers were found; the other six studies, including three that were performed in the same 17 patients 2 years before the cancers were found and three that revealed a coexisting benign nodule (diameter, 4–5 mm), were not used in this investigation. All 17 cancers were adenocarcinomas. At low-dose CT, six nodules had pure GGO, 10 nodules had mixed GGO, and one nodule had solid opacity. The mean diameter of the 17 missed cancers was 10 mm (range, 6–17 mm). Fifteen studies in which cancer was missed due to interpretation errors were also excluded from the observer study. In addition, we included studies obtained in 10 control subjects (five men and five women;

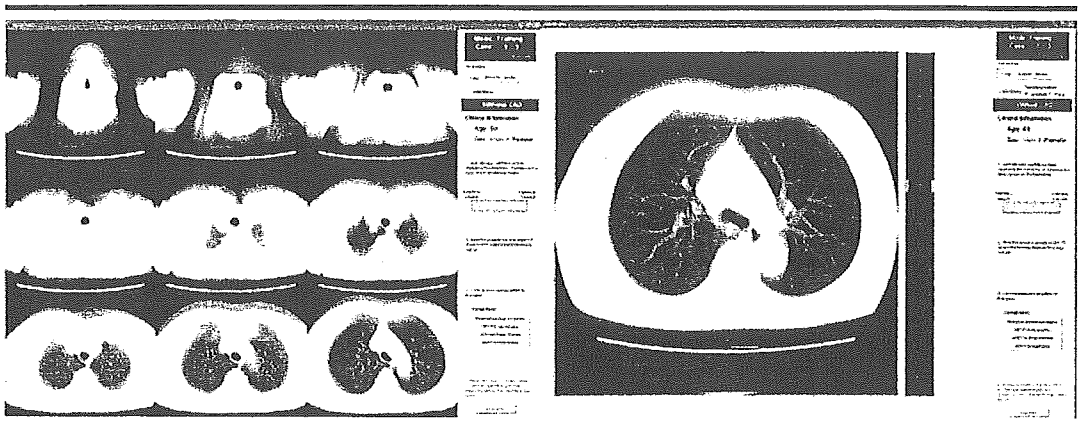


Figure 1. (a) Example of the multiformat display used by the six radiologists in group 1. From the top to the bottom of the entire lung for each patient, 27 consecutive transverse CT sections were displayed in a multiformat (3 × 3) mode on three high-spatial-resolution monitors. (b) Stacked cine-mode display used by the eight radiologists in group 2. Magnified and stacked transverse CT sections were displayed on one monitor.

TABLE 1
A_z Values for 14 Radiologists in Detection of Missed Cancers without and with CAD Scheme

Group and Observer	A_z Value	
	Without CAD	With CAD
Group 1*		
1	0.856	0.962
2	0.792	0.825
3	0.613	0.824
4	0.723	0.865
5	0.851	0.876
6	0.706	0.818
Group 2†		
7	0.589	0.828
8	0.723	0.834
9	0.818	0.824
10	0.865	0.936
11	0.811	0.899
12	0.826	0.856
13	0.786	0.822
14	0.728	0.784
All observers	0.763	0.854

Note.—The difference in A_z values without and with the CAD scheme was statistically significant, with a P value of .002 for all radiologists, .04 for group 1, and .01 for group 2. No statistically significant difference in A_z values between the two viewing modes was found for observers without and with the CAD scheme.

* This group used a multiformat display. The mean A_z value for this group without CAD was 0.757; the mean value with CAD was 0.862.

† This group used a cine-mode display. The mean A_z value for this group without CAD was 0.768; the mean value with CAD was 0.848.

mean age, 63 years; age range, 49–69 years) without cancer who had participated in the same screening program and whose ages and sexes closely matched those of the patient group; findings in these subjects were confirmed with 2-year follow-up. Some of the 27 studies revealed other abnormal findings such as scars, focal interstitial lung lesions, and small (<3 mm) benign nodules. The CAD scheme had a sensitivity of 82% (14 of 17 cancers), with 3.0 false-positive findings per study (range, zero to eight) for patients with missed cancers and 2.4 false-positive findings per study (range, zero to five) for the 10 control subjects (7,8).

Two image display formats were used in this investigation: a multiformat display and a "stacked" cine-mode display (Fig 1). For the multiformat display, from the top to the bottom of the entire lung for each patient, 27 consecutive sections with the original matrix size at low-dose CT were displayed in a multiformat display (3 × 3) on three high-spatial-resolution (1600 × 1200 pixels) liquid crystal display color monitors (CCL202; Totoku Electric, Tokyo, Japan). For cine-mode display, the same 27 CT sections for each study were magnified and stacked on one monitor. The speed or sequence of the image display for cine-mode display was controlled manually by the observer. The windowing in the two image display formats was initially set at lung settings but could be adjusted by the observer to bronchial or mediastinal settings. Two clinical parameters (age and sex) were provided to the observer on the monitor.

The 14 radiologists who participated in this observer study were classified into two groups according to type of display. Observers who used multiformat display (group 1) consisted of five general radiologists with 7–18 years of experience (mean, 12 years) and one 3rd-year radiology resident. Observers who used cine-mode display (group 2) consisted of three chest radiologists with 16, 17, and 45 years of experience (mean, 26 years), four general radiologists with 5–16 years of experience (mean, 13 years), and one 4th-year radiology resident. The observers in group 2 had more experience than did the observers in group 1.

Radiologists were given the following instructions: "*(a)* We wish to evaluate radiologists' performance in detecting lung cancer without and with a CAD scheme on low-dose CT scans obtained from a screening program. *(b)* The role of the CAD output is that of a 'second opinion.' *(c)* Twenty-seven low-dose CT studies (with 10-mm-thick sections) that did not or did contain lung cancer and/or noncancerous abnormalities such as benign nodules and scars are included in this observer study. *(d)* The observer in this study will be blinded to the number of patients with lung cancer and the performance level of the CAD scheme. *(e)* Click on the screen by using a mouse (i) to indicate on a bar your confidence level regarding the presence (or absence) of a lung cancer and (ii) to locate the most likely position on each CT scan. You may indicate the cancer location first and *(f)* click on one of the following four clinical actions: (i) Return to annual screening, (ii) diagnostic thin-section CT in 6 months, (iii) diagnostic thin-section CT in 3 months, or (iv) diagnostic thin-section CT immediately." The radiologists made their judgments first without and then with the CAD scheme.

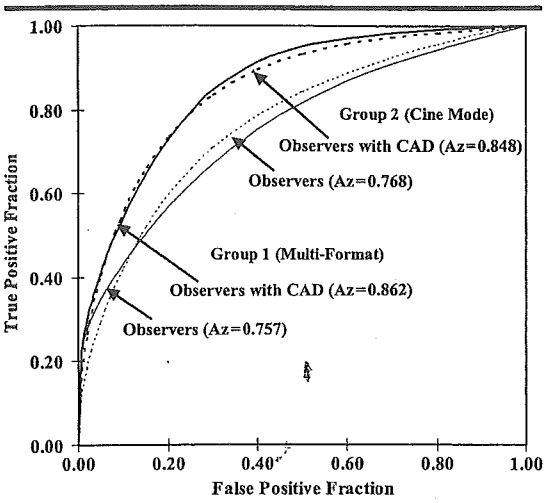


Figure 2. Graph shows ROC curves for detecting cancers missed at CT without and with use of the CAD scheme and for the two display modes. With the CAD scheme, the average A_z value improved significantly from 0.757 to 0.862 for group 1 (P = .04) and from 0.768 to 0.848 for group 2 (P = .01).

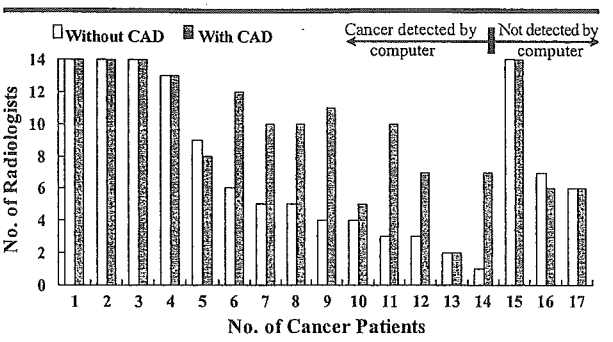


Figure 3. Bar graph shows the number of radiologists who correctly detected cancer in each of 17 patients with lung cancer with and without the use of the CAD scheme. In eight patients, the CAD scheme had a beneficial effect for one to seven radiologists. In two patients, the use of CAD had a detrimental effect for two radiologists. (See details in Discussion.)

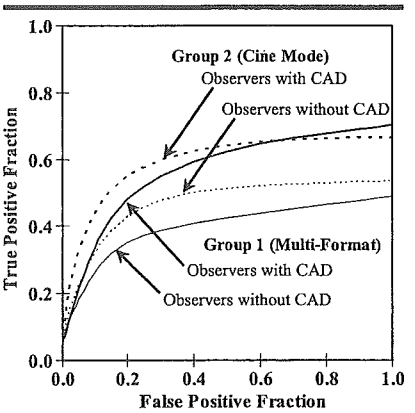


Figure 4. Graph shows LROC curves in the detection of cancers missed at CT for radiologists with and without use of the CAD scheme and with two display modes. The LROC curve was improved for groups 1 and 2 with use of the CAD scheme.

For a training session before the test, we provided five different cases (that were not part of the study set of 27) so that radiologists could learn how to operate the cine-mode interface and how to take into account the computer output in their decision. The reading time was not limited in this study. The average reading time was 48 minutes (range, 27–61 minutes; 1.8 minutes per case).

Statistical Analysis

The confidence level ratings from each observer were analyzed with use of the receiver operating characteristic (ROC) method, and a quasi-maximum-likelihood estimation of the binormal distribution was fitted to the radiologists' confidence ratings (11). The statistical significance of the difference in the area under the ROC curve (A_z) between observer readings without and with the CAD scheme was tested with use of the Dorfman-Berbaum-Metz method (12), which included both reader variation and case sample variation by means of an analysis of variance approach. Localization ROC (LROC) curves (13) for observers without and with the CAD scheme were also determined for each reading condition.

The "proper" binormal model (14) was used to fit the ROC and LROC curves (Metz CE, written communication, 2004). In this study, localization was considered correct if the center of the cancer lesion was located within 15 mm from the point marked by the observer. The distance criterion of 15 mm was based on the fact that our database contained lesions with diameters as large as 26 mm. The distance was computed automatically by the user interface program. The sensitivity in this study was defined on the basis of the number of cancer lesions that were correctly located by an observer regardless of the confidence level ratings. The statistical significance of the difference in sensitivities between the computer outputs and the observer readings without and with the CAD scheme was tested by means of a confidence interval method by taking into account reader variation alone (15). The statistical significance of the difference in sensitivities between radiologists without and with the CAD scheme and in clinical actions between a beneficial and a detrimental effect of the CAD scheme for each of the studies that did or did not contain a lung cancer was estimated with use of the Student paired t test for the 14 radiologists. In general, $P < .05$ was considered to indicate a statistically significant difference.

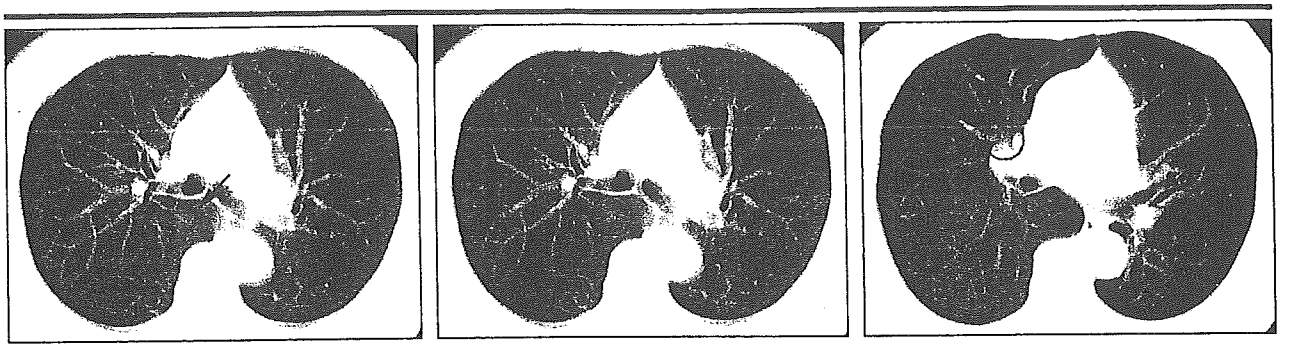
RESULTS

Radiologist Performance

With use of the CAD scheme, the average A_z value improved significantly from 0.763 to 0.854 for the 14 radiologists (P = .002), from 0.757 to 0.862 for group 1 (P = .04), and from 0.768 to 0.848 for group 2 (P = .01) (Table 1, Fig 2). No significant difference in the average A_z values between the two groups was found for radiologists without (P = .82) and with (P = .63) CAD.

In eight of the 17 patients with lung cancer, the CAD scheme helped from one to seven radiologists find the cancers (Fig 3). In two patients, CAD had a detrimental effect for two radiologists. The average LROC curves for the 14 radiologists without and with the CAD scheme in the two groups are shown in Figure 4. Figure 5 shows images from a patient in whom the use of CAD helped seven radiologists detect a cancer lesion.

With use of the CAD scheme (sensitivity, 82% [14 of 17 cancers]), the average sensitivity in the detection of 17 cancers improved significantly—from 52% (124 of 238 observations) to 68% (163 of 238 observations) for the 14 radiologists ($P <$



a. b. c.

Figure 5. Images obtained in a 69-year-old woman in whom CAD was helpful. Transverse CT scans show (a) a missed lung cancer (arrow) with pure GGO in the right upper lobe, (b) the cancer, and (c) a false-positive finding. Circles in b and c indicate the computer detections. In this patient, 10 radiologists did not detect the cancer without CAD, whereas CAD helped seven radiologists find the cancer.

TABLE 2
Number of Patients in Whom Important Clinical Action Related to Follow-up Was Changed by 14 Radiologists Owing to CAD

Observer No.	Patients with CAD-revealed Lung Cancer*		Patients without Lung Cancer†	
	Beneficial Effect	Detrimental Effect	Beneficial Effect	Detrimental Effect
1	2	0	0	1
2	2	1	0	0
3	3	1	0	0
4	5	0	1	0
5	0	0	0	0
6	6	0	1	0
7	2	0	0	0
8	2	2	0	0
9	0	0	0	0
10	0	0	0	0
11	5	0	0	0
12	1	0	0	1
13	0	0	0	1
14	2	0	1	0

Note.—"Beneficial effect" indicates a change to follow-up for a patient with lung cancer and a change to screening for a patient without lung cancer; "detrimental effect" indicates a change to screening for a patient with lung cancer or a change to follow-up for a patient without lung cancer.

* The mean number of such patients in whom the use of CAD had a beneficial effect was 2.1 ± 2.0 (standard deviation); the mean number in whom it had a detrimental effect was 0.3 ± 0.6. The difference between a beneficial effect and a detrimental effect among these patients was statistically significant ($P = .005$).

† Patients in whom CAD revealed a condition other than lung cancer. The mean number of such patients in whom the use of CAD had a beneficial effect was 0.2 ± 0.4; the mean number in whom it had a detrimental effect was also 0.2 ± 0.4.

.001), from 49% (50 of 102 observations) to 71% (72 of 102 observations) for group 1 ($P = .02$), and from 54% (74 of 136 observations) to 67% (91 of 136 observations) for group 2 ($P = .006$). The sensitivity of the CAD scheme alone was greater than that of the radiologists alone ($P < .001$) and that of the radiologists with CAD ($P < .001$), although the specificity was lower. No significant difference in sensitivities was found between the two viewing modes for radiologists without ($P = .44$) and with ($P = .71$) the use of CAD.

Clinical Actions

For the four clinical actions described earlier (ie, return to annual screening or perform diagnostic thin-section CT in 6 months, 3 months, or immediately), we attempted to quantify the changes in clinical action attributable to use of the CAD scheme. For patients with a lung cancer, the average number for whom clinical actions were changed for a beneficial effect (ie, a "step up") (3.3) was greater than the number for whom clinical actions were changed for a detrimental effect (ie, a "step down") (0.4) ($P < .001$). For patients without a lung cancer, the average numbers affected by the CAD scheme for a beneficial effect (step down) and a detrimental effect (step up) were 0.5 and 0.3, respectively ($P = .27$).

Table 2 shows the number of patients for whom the important clinical action related to follow-up was influenced positively or negatively by the 14 radiologists. For these patients, the difference between the mean number of patients in whom the action was changed from screening to follow-up (2.1 patients) and the mean number of patients in whom the action was changed from follow-up to screening (0.3 patients) was significant ($P = .005$). For patients without a lung cancer, no statistically significant difference between a beneficial effect (a change from follow-up to screening [in 0.2 patients]) and a detrimental effect (a change from screening to follow-up [in 0.2 patients]) owing to use of the CAD scheme was found for the radiologists ($P > .99$).

DISCUSSION

It has been reported (16–21) that the use of CAD has the potential to improve diagnostic accuracy in the detection of lung nodules on chest radiographs and CT scans. In previous studies with chest radiography, however, some abnormal cases—each with one lung nodule—and some normal cases were used for the observer test, and the radiologists' performance in terms of their confidence level regarding the presence or absence of a nodule was evaluated by means of ROC analysis without localization (16,17). For developing CAD schemes for use with relatively thick (18,19) or thin CT sections (20,21), the number of lung nod-

ules was generally not limited to a single nodule in each examination, and the sensitivity with which radiologists correctly detected the nodule, regardless of the confidence level, was commonly used as a measure of the radiologists' performance. In previous CT-based studies (18–21), the truth for the nodules was established by radiologist consensus—not according to pathologic results—because most small nodules are benign and do not undergo biopsy or resection.

There were some differences between the present study and the previous studies, as follows: In the present study, *(a)* the CAD scheme was developed by using missed lung cancers, which were confirmed at surgery; *(b)* the mean diameter of the cancers was 12 mm (all were at least 6 mm), and the CT findings for the cancers included lesions with pure GGO, mixed GGO, and solid opacity; and *(c)* ROC, LROC, and sensitivity analyses were used to evaluate radiologists' performance in the detection of subtle cancers without and with CAD. The importance of these differences is discussed in the next paragraphs.

Missed lung cancers include the most difficult cases for detection in clinical work and mass screening programs, and several investigators have reported the possible reasons for missing lung cancers on CT scans (4,5,22,23). In our series (5), lung cancers were missed mainly because they had low attenuation (eg, they were of small size and/or were faint lesions with GGO) or because of the presence of large structured noise elements (normal structures and/or complex backgrounds caused by other disease) or both. In addition, the cancers had poor conspicuity as defined by Kundel and Revesz (24). In general, the missed cancers corresponded to earlier visible findings in the same locations at previous examinations—findings that had been identified as abnormal according to radiologists' consensus. However, in a previous study by Austin et al (25) of radiologists' performance alone, each of six radiologists, who were biased by knowledge that the patients had lung cancers that were missed on chest radiographs, missed cancer in a mean of 26% of 22 patients. The main purpose of our study was to identify whether unassisted radiologists could identify these previously missed cancers in the context of an observer study and to evaluate whether a CAD scheme could help them detect the cancers missed on CT scans.

Diederich et al (26) reported that more than 70% of noncalcified nodules are 5 mm or smaller, and no lung cancers were found among those small lesions in CT screening programs for lung cancer at baseline. Similar findings have also been reported by Swensen et al (27). Henschke et al (28) reported that the frequency with which malignancy was or could have been diagnosed when the largest noncalcified nodule was smaller than 5 mm in diameter was very low (0 of 378). The nodules with pure or mixed GGO on CT scans in lung cancer screening programs were more likely to be malignant than were solid nodules (29,30). Although there was a limitation in the low-dose CT protocol with 10-mm-thick sections used in our study, the cancers were at least 6 mm in diameter, and the CT findings for the cancers included lesions with pure GGO, lesions with mixed GGO, and lesions with solid opacity. We believe, therefore, that it may be more important for a CAD scheme used as a "second opinion" to detect relatively large nodules with or without GGO; such nodules include primary lung cancers more frequently than small nodules, most of which are benign lesions, do.

Basically, ROC analysis without localization (11,12) can help correctly evaluate observer performance in the detection of the presence (or absence) of a lesion on medical images when each image does not include obvious false-positive findings, provided that the number of patients is sufficiently large. However, because chest CT scans may contain pulmonary vessels or focal lung diseases that have an appearance that is similar to that of nodular lesions, high positive confidence level ratings by radiologists for a given CT study do not always correspond to true-positive findings (lung cancers) but instead sometimes correspond to false-positive findings. With use of LROC analysis (13), only the responses with correct localization are evaluated for each reading condition, although a proper statistical test for practical use in evaluating the difference between the curves is still unavailable. The shortcoming of LROC analysis for estimating sensitivity is that the radiologist's performance is evaluated only for patients with true-positive findings and not for patients with true-negative findings. Therefore, in this study, we decided to evaluate the performance with three methods—that is, ROC, LROC, and sensitivity analysis—and the results obtained with all three methods showed that the diagnostic accuracy of the radiologists improved with use of the CAD scheme.

Although the radiologists in our study were able to recognize the presence of some subtle lung cancers, they could not be sure whether the CT features of the lesion were indicative of malignancy even when the computer marked the lesion. The possible reasons why the sensitivity for radiologists who used CAD did not reach at least 82% include the fact that the radiologists were not familiar with the appearance of early lung cancers at CT, especially at thick-section CT. In addition, the sensitivity of the radiologists for detecting cancer lesions was affected by some findings such as scars and vertically oriented pulmonary vessels, which had an appearance similar to that of nodular lesions on CT scans in this observer study. In addition, false-positive computer findings would have an effect on radiologists' performance in the detection of lung cancer. We noted that radiologists tended to ignore the CAD output more frequently for studies with a large number of false-positive findings (eight per study, the largest in our scheme) than for those with a small number of false-positive findings. In a previous observer study of the use of LROC analysis in the detection of clustered microcalcifications on mammograms, Chan et al (31) reported that radiologists' diagnostic accuracy with CAD was further improved by reducing the computer's false-positive rate (from four to one false-positive finding per image).

In this observer study, the use of CAD had a detrimental effect in two patients for two radiologists. In one patient, a radiologist detected a cancer lesion without CAD with a confidence level of 0.46 and made a recommendation to follow up the cancer with diagnostic thin-section CT in 3 months. The computer indicated the cancer lesion and eight false-positive findings. With use of CAD in the same patient, a different radiologist changed the location from cancer to a false-positive finding (vertical pulmonary vessel) with a confidence level of 0.59 and did not change the clinical action. In another patient, another radiologist detected a cancer lesion without CAD with a confidence level of 0.31 and recommended follow-up with CT in 6 months. The computer did not mark the cancer lesion but indicated three false-positive findings. The radiologist who used CAD also changed the location from cancer to a false-positive finding (vertical pulmonary vessel) with a confidence level of 0.46 and did not change the clinical action. Therefore, when the CAD scheme yields false-positive findings that are very

similar to true-positive findings, it may have a detrimental effect on the observers' performance when the task involves the detection of only one lesion at CT in an observer study. If radiologists were allowed to identify more than one lesion in an observer study, however, it is possible that they might elect to keep the cancer as detected initially and add the false-positive finding as a further suspicious area.

In recent CT screening programs, most images were reviewed in a multiformat display (film- or monitor-based viewing) and/or a cine-mode display (1–3,26,27). The cancers in this observer study were missed in the Nagano lung cancer screening project, in which a multiformat display (3 × 4 or 4 × 4) on two high-spatial-resolution (1728 × 2304 matrix) monitors was used (5). A similar multiformat viewing mode was used in our study by the radiologists in group 1. In general, cine viewing of CT scans of the chest is believed to improve radiologists' ability to detect lung nodules compared with film-based viewing (32,33). Tillich et al (33), however, found no significant difference between cine and film-based viewing in the detection rate of pulmonary nodules (metastases) larger than 5 mm in diameter. We also did not find a significant difference between the two viewing modes in the detection of primary lung cancers (≥6 mm) missed in a CT screening program. The limitations of this study include the facts that the low-dose CT sections were thick (10 mm), rather than thin, and the radiologists differed in the two groups. It was not the purpose of our study to compare diagnostic accuracy with the cine or multiformat mode but rather to determine that the benefits of CAD were substantial, independent of the display mode used.

In summary, lung cancers missed at low-dose CT screening were very difficult to detect, even in an observer study; the use of CAD, however, improved the radiologists' performance in the detection of these subtle cancers. In addition, CAD can help radiologists make recommendations for follow-up.

Acknowledgments: The authors are grateful to Ulrich Bick, MD, Alexandra Funaki, DO, John Fennessy, MD, Gen Iinuma, MD, Edward Michals, MD, Masaki Matsusako, MD, Peter MacEneaney, MD, Sidney Regalado, MD, Christopher Straus, MD, Gregory Scott Stacy, MD, Shuji Sakai, MD, Taylor Stroud, MD, Ira Wolke, MD, and Chaotong Zhang, MD, for participating as observers; to Charles E. Metz, PhD, and Lorenzo Pesce, PhD, for the use of proper binormal model in ROC and LROC curves; and to Elisabeth Lanzl, AM, for improving the manuscript.

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Subcentimeter Large Cell Neuroendocrine Carcinoma of the Lung

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Abstract: To our knowledge, no report exists of a subcentimeter size large cell neuroendocrine carcinoma (LCNEC) of the lung. A 75-year-old man participating in a low-dose CT screening program for lung cancer was found incidentally to have a partly-solid nodule in the right upper lung. After treatment with antibiotics, a repeat CT showed resolution of the nodule, but a new solid nodule measuring 9 × 9 mm was detected in the left lower lobe. The lesion showed marked enhancement on dynamic contrast-enhanced MRI. Video-assisted thoracic surgery and frozen section biopsy was suggestive of malignant lesion, resulting in extension of surgery to lobectomy with nodal dissection. The final diagnosis was stage IA-LCNEC. The estimated volume doubling time of the tumor was 30.1 days. These aggressive tumors may rarely have doubling times that overlap with benign processes.

Key Words: large cell neuroendocrine carcinoma, CT screening, peripheral small lung cancer, rapid growth, volume doubling time

(*J Thorac Imaging* 2005;20:288–290)

It is not uncommon to find small nodules in the peripheral lung zone in asymptomatic individuals on mass screening for lung cancer using low-dose chest computed tomography (CT). We previously reported that a CT screening program increases the detection rate of primary lung cancer by about 10-fold compared with screening using chest radiographs.[1] However, there is controversy regarding the interval between repeat CT screening, although there seems to be some agreement on annual repeat CT screening. Before a decision is made on the interval, there is a need to accumulate information regarding the benefits associated with such interval in detecting lung cancers at a surgically curable stage with a wide range of growth rates. We report here a patient who was incidentally found to have a subcentimeter size rapidly growing nodule that proved to be large cell neuroendocrine carcinoma (LCNEC) in the left lung. The tumor was incidentally detected at the time of repeat work up CT on the conventional CT image that was taken prior to high-resolution CT (HRCT) to examine a low-dose CT screened-nodule in the right lung.

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CASE REPORT

A 75-year-old current smoker (68 pack-year) asymptomatic man underwent annual low-dose CT screening in September 2003, followed by high-resolution CT (HRCT) 2 weeks later for a new 6 × 8 mm partly-solid nodule in the periphery of the right upper lobe. After 1-month of antibiotic treatment (ciprofloxacin 600 mg/d), a repeat HRCT showed partial resolution of the nodule. A third HRCT performed 3 months later following the second HRCT showed further resolution. Complete resolution of the nodule was confirmed on the fourth HRCT, performed 7 months after the initial HRCT.

On that occasion, a solid nodule measuring 9 × 9 mm in diameter with homogeneous soft tissue density and a well-defined margin was newly identified in the periphery of the left lower lobe (Fig. 1B). A careful retrospective re-examination of the conventional CT taken 3 months earlier, at the occasion of third work up CT examination, showed a tiny (4 × 4 mm diameter) lesion (Fig. 1A). Based on the measurements of the nodule on CT images, the tumor volume doubling time (VDT) was estimated at 30.1 days using the method described by Hasegawa et al.[2] Lung tumor markers, including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and pro-gastrin-releasing peptide (Pro-GRP) were within the normal range. After a 1-month course of antifungal treatment of a possible fungal infection (itraconazole, 200 mg/d), follow-up HRCT showed tumor growth with additional pleural tag formation (Fig. 1C). Gadolinium-enhanced magnetic resonance imaging (MRI) showed definite enhancement effect of the nodule, suggesting an active lesion. The nodule was biopsied by video-assisted thoracic surgery (VATS), and intraoperatively diagnosed as a malignant tumor (frozen-section method). Based on a provisional diagnosis of a rapidly growing cancer with highly proliferative activity on CT images, a complete lobectomy with nodal dissection (ND) 2a was performed. The postoperative course was uneventful.

The final pathologic diagnosis was stage IA-large cell neuroendocrine carcinoma, measuring 8 × 10 mm, p0, pm0, n0, and p-T1N0M0. Histopathological examination of hematoxylin-eosin stained sections showed an organoid pattern, nuclear palisading pattern, central necrosis, and abundant mitosis in the cancerous tissue with no invasion of the surrounding vasculature or lymphatic vessels (Fig. 2A). Immunohistochemistry showed positive staining for chromogranin A and S-100 (Fig. 2B), but negative for NSE.

DISCUSSION

LCNEC was added to the World Health Organization (WHO) classification of lung tumors in 1999. The aggressive clinical behavior and poor prognosis of LCNEC are well documented,[3,4] and novel therapeutic approaches are needed.

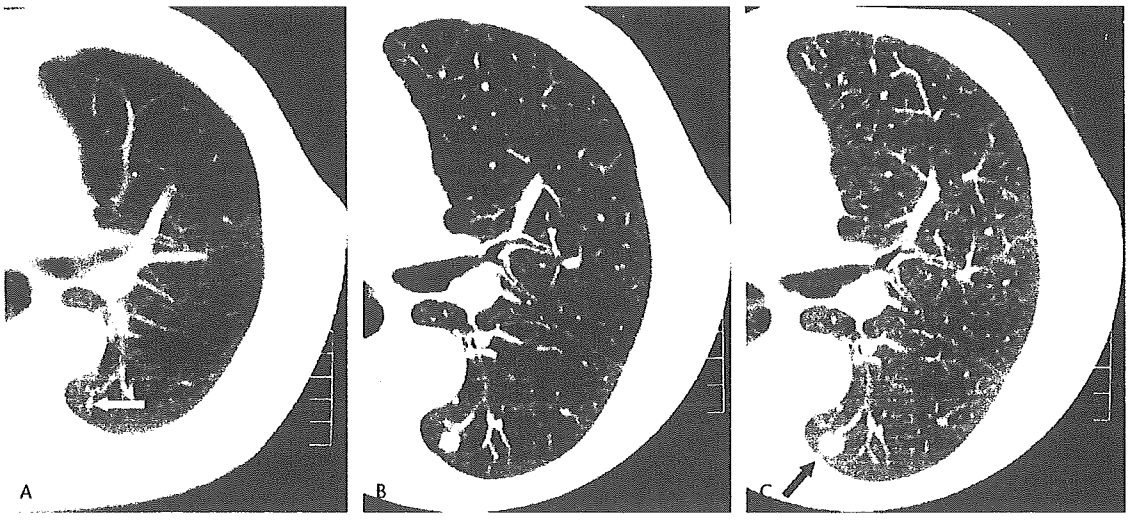

FIGURE 1. Computed Tomographic scan. A, The tumor appears as a tiny (4 × 4 mm) lesion in the periphery of the superior segment of the left lower lobe, which was identified retrospectively on a conventional CT image taken 3 months prior to that shown in (B). White arrow points to the tiny lesion. B, In this high-resolution CT (HRCT), the solid nodule was first recognized as a 9 × 9 mm sized, homogeneous one of soft tissue density with well-defined margin. C, Further growth of the lesion with additional pleural tag formation on HRCT taken 1 month after the image displayed in (B) following a 1-month course of anti-fungal treatment. Arrow shows the pleural tag.

LCNEC constitutes a minority of lung cancers, for example, only 2 cases out of a total 106 resected non-small cell lung cancers (1.9%) in our hospital during the last 4 years. Furthermore, resected subcentimeter LCNEC is extremely rare,[5] even in the CT-screening era.[6] Although the prognosis of patients with resected LCNEC is reported to be poorer than patients with the same stage of poorly differentiated non-small cell lung cancer and other large cell carcinoma even in stage I-disease,[3] because of the highly aggressive biologic behaviors,[7] complete resection of a subcentimeter LCNEC that is still in stage I is expected to be better than that in other stages.[4]

CT allows us to identify rapidly growing lung cancers like LCNEC in the localized stage so that surgery can be performed while the tumor is still in a curable stage. Follow-up and HRCTs within the context of a screening program may allow the incidental identification of rapidly growing lung tumors. The VDT of the LCNEC in our patient was 30.1 days, representing the most rapidly growing tumor of CT-screened lung cancers reported so far (for example, mean ± SD; adenocarcinoma 533 ± 381 days; squamous cell carcinoma, 129 ± 97 days; small cell carcinoma, 97 ± 46 days).[2] Such a short VDT is compatible with the aggressive

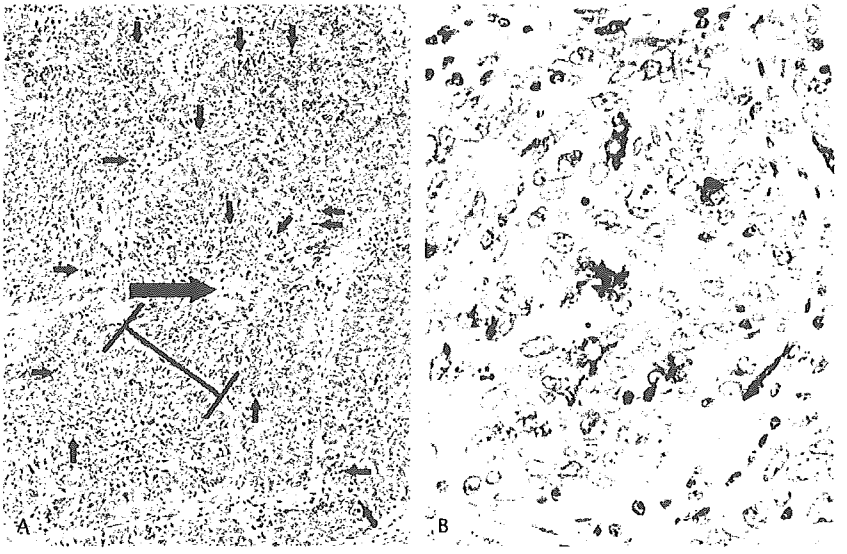

FIGURE 2. Histopathological findings. A, Note the presence of large mitotic cancer cells pointed to by small arrows, with organoid structures, central necrosis pointed to by a large arrow, and nuclear palisading patterns indicated by |—|. Magnification, ×10. B, Positive immunostaining for S-100 protein. Magnification, ×40.

clinicopathologic[3] and molecular biologic features of LCNEC reported previously.[7] Detection of subcentimeter tumors by CT scan may be the most critical point in saving the life of patients with LCNEC.

As to the interval between repeat CT screening to detect lung cancers at a surgically curable stage, although there seems to be some agreement on annual repeat CT screening, which has a length-time bias for detecting slower growing tumors and may exhibit a lower detection rate of rapidly growing tumors at a curable stage, which are more likely to be symptom-detected, repeat CT screening may become feasible at an appropriate interval to find cancers more effectively based on the detection rate, cost, radiation exposure, and curability. There is a need to accumulate more information regarding the benefits associated with such an interval to learn about clinical management approaches, presently mainly based on the surgical treatments, for such small solid lung cancer.

ACKNOWLEDGMENTS

The authors thank Ms. Kimberly K. Agnello and Prof. Claudia I. Henschke, Lung Cancer Screening Program, Department of Radiology, Weill Medical College, Cornell University, New York, for their help in the preparation of the manuscript.

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Minority Opinion

CT Screening for Lung Cancer

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(*J Thorac Imaging* 2005;20:324–325)

The Society of Thoracic Radiology (STR) charged Dr. Stephen Swensen to form a committee to develop a consensus statement on screening for lung cancer. After numerous discussions, a consensus could not be reached. Instead, the STR decided to publish the majority opinion (this issue, page 321) and to allow me, as the dissenting opinion, to write this editorial.

While we agreed with point 1 of the majority consensus statement, we disagree with points 2–5 in the STR consensus statement as detailed below, and we also provide an alternative statement.

Majority Point 2: Screening for lung cancer with chest radiography has not been shown to lower disease-specific mortality. CT screening offers hope for earlier detection that could lower disease-specific mortality; it is unproven.

In the United States, the evidence against screening chest radiography is essentially based on a single 30-year-old study, the Mayo Lung Project. Moreover, it has been recognized generally that this study was flawed[1–3] and should not be used as a basis for public policy. Recently the American Cancer Society[4] and then the United States Preventive Services Task Force[5] have changed their previous recommendation against screening for lung cancer to one advising people to discuss the potential risks and benefits with their physician. The United States Preventive Services Task Force based its change on 6 case-control studies on screening using chest radiography in Japan, which showed a small, but real, benefit when compared with no screening.[5] Because the evidence now suggests a benefit for chest radiography screening, at least one sufficient to change the recommendations, a better diagnostic test should be of even greater benefit. CT provides for diagnosis of smaller, earlier lung cancers, as shown in multiple studies,[6–11] and its promise was used as a justification for the National Lung Screening Trial (NLST).[12]

Majority Point 3: Concerns have been raised regarding false-positive diagnoses, over diagnosis, cost, and morbidity and mortality related to intervention.

While these are important considerations for any screening program, numerous publications have shown that a well-thought-out regimen of CT screening can keep these at an acceptable level.[6–11,13–15] Thus, the real issue for high-quality screening is that a regimen should be used and adhered to as a matter of quality assurance.

To highlight one example, consider the issue of false-positives. The NLST defines all non-calcified nodules ≤4 mm to be a negative result of screening,[12] and I-ELCAP protocol calls for 1-year repeat screening when all non-calcified nodules are <5 mm in baseline screening.[8,16] Given either of these definitions, the majority of false-positives are eliminated. Similarly, all the other issues mentioned can be addressed and quantified.[8,17]

Majority Point 4: Promotion of CT screening to the general population by medical professionals with a financial interest in an enterprise is inappropriate.

This issue, we feel, is beyond the scope and expertise of our professional society, which focuses on thoracic radiology and not on public health or private practice policies and related economic issues. But, it should be noted that all academic radiologists also have an interest in the financial well-being of their department and institution.

We do not advocate CT screening for lung cancer to the general population, but we, as well as others,[3–5] consider it reasonable for a person at high-risk for lung cancer to be screened at an institution with sufficient experience in screening using an appropriate regimen of screening with quality assurance measures in place.

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Majority Point 5: There is insufficient evidence to justify recommending CT screening for lung cancer to patients, including those at high risk for lung cancer.

As stated above, we believe there is sufficient evidence for it to be reasonable for a person at high-risk for lung cancer with a sufficient life expectancy to pursue screening.

There is a growing body of evidence collected over the past 12 years that CT screening for lung cancer leads to a dramatic increase in the proportion of early stage genuine (fatal in the absence of early treatment) lung cancer relative to symptom-prompted diagnosis.

The proposed alternative statement is:

1. Lung cancer is the most common cause of cancer death in both men and women in the industrialized world. It, thus, is a major public health problem.[18,19]
2. Prior studies on screening for lung cancer were interpreted as not demonstrating a benefit of screening, but it is generally agreed that there were shortcomings in the methodology of those studies.[1–5]
3. It is accepted that the curability of Stage I lung cancers is very high relative to the curability of late-stage cancers; and within Stage I, cancers less than 3 cm in diameter (Stage IA) are more curable than those that are larger (Stage IB).[20,21]
4. Studies on annual CT screening have established that lung cancers are much more commonly diagnosed at Stage I and at smaller sizes than by chest radiography.[6–11]
5. Based on the points above, it is knowable that annual CT screening for lung cancer provides for prevention of death from lung cancer by early intervention. Quantitative assessment of the actual magnitude of this benefit is being pursued by studies in the US and elsewhere.
6. A person at high-risk for lung cancer yet free of suspicion-raising symptoms of it, who is interested in potentially being screened, should be fully apprised of the implications of screening and of the treatment that may result. In light of this, it is reasonable for the individual to choose to be screened by a suitably defined CT regimen.[22]

Point 5 follows from Points 3 and 4. Point 6 draws from point 5 together with the principle of Patients' Autonomy, recently enunciated by a prestigious European-US joint commission.[22]

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Respiratory Medicine (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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Clinical differences in the Global Initiative for Chronic Obstructive Lung Disease Stage 0

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Received 17 June 2005; accepted 26 November 2005

KEYWORDS
COPD;
Stage 0;
Smoker;
Visual score;
Low-dose chest computed tomography;
Pulmonary function data

Summary This study was to examine the clinical differences between Stage 0 and normal subjects, using low-dose chest computed tomography (CT) and pulmonary function tests. Enrolled subjects performed as a health check for lung cancer screening including low-dose CT and pulmonary function tests. Subjects were divided into Stage 0, chronic obstructive pulmonary disease according to pulmonary function tests, and normal subjects. The severity of emphysema (visual score) was calculated on three low-dose CT slices. Low-dose CT and pulmonary function tests were performed in 1359 men and 888 women. The numbers and percentages of men and women smokers were 1076 (79.2%), and 107 (12.0%), respectively. A total of 722 individuals had one or more respiratory symptoms, such as cough (69.8%), sputum (75.8%), or shortness of breathing (0.83%). Of the 722 subjects, 71 (9.8%) individuals satisfied the criteria of chronic respiratory symptoms. Among the normal subjects, smoking caused differences in airflow limitation as a result of pulmonary function tests. The proportion of smokers and the visual score were significantly higher in Stage 0 than those in the normal subjects. The percentages of the maximal mid-expiratory flow (%MMF) and of the peak expiratory flow rate were significantly lower in Stage 0 than in the normal subjects. %MMF and the proportion of visual score were significantly lower in the smoking Stage 0 than in the nonsmoking Stage 0 subjects. Smoking would indicate early signs of emphysematous change between Stage 0 and normal subjects in comparison of pulmonary function tests and visual score of low-dose CT.

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doi:10.1016/j.rmed.2005.11.021

Introduction

Chronic obstructive pulmonary disease (COPD) has been forecast to be the third leading cause of death in the world by 2020 because of the global increase in smoking.[1] Recently, a Japanese epidemiological study indicated that over 5,300,000 Japanese people (approximately 8.5% of the total population) may suffer from COPD.[2] However, the number of patients receiving treatment for COPD was only approximately 210,000. Many people who develop COPD are smokers, and their pulmonary function decreases more rapidly than that of nonsmokers.[3,4] COPD is normally diagnosed by pulmonary function tests, which are often used for the initial diagnosis and assessment of severity of emphysema. However, COPD is an insidious disease, with many years intervening between the development of pulmonary dysfunction and the onset of serious respiratory symptoms, such as severe breathlessness.

Many studies have indicated that smoking is the major environmental factor contributing to the decrease in pulmonary function. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lung's total burden of inhaled particulates and gases.[5] Cessation of cigarette smoking does not necessarily result in the recovery of the level of pulmonary function but it is associated with slower rates of decline in pulmonary function.[6,7] Moreover, cessation of cigarette smoking can improve the survival prospects of middle-aged smokers over the entire range of pulmonary function.[8] Smoking reduction meaning a reduction in the number of cigarettes smoked per day; however, this is associated with a small increase in risk as compared with sustained heavy smokers.[9]

Cigarette smoke has direct toxic effects on bronchial epithelial cells and alveoli, and the pathological changes include mucus hypersecretion, ciliary dysfunction and airflow limitation. Mucus hypersecretion and ciliary dysfunction are related to chronic cough and sputum production. These symptoms are often present for many years before the development of other more serious symptoms (shortness of breath, dyspnea) or pathological abnormalities. The classification of severity based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) includes Stage 0, which includes subjects at risk of developing COPD late in life.[10] Subjects in the Stage 0 group complain of chronic cough and sputum production but have no airflow obstruction, as defined by a decrease in forced expiratory volume in 1 s (FEV_1). Active smoking is strongly associated with chronic cough and sputum production. Therefore, the most effective intervention is to stop smoking, preferably at an early stage, such as of Stage 0.[3]

Screening the general population for the respiratory symptoms of Stage 0 is effective but not feasible in the daily routine of a general practice. However, Stage 0 includes patients with other respiratory diseases, such as bronchial asthma, chronic bronchitis, etc. As a result, many individuals who have other underlying diseases are included in Stage 0. It is necessary to promote the cessation of smoking as a means of early intervention in Stage 0 subjects. The present study was performed to examine the clinical differences between Stage 0 subjects, i.e., those defined as "at risk" of COPD and normal subjects, using clinical information, low-dose chest computed tomography (CT) scan and pulmonary function tests.

Materials and methods

Our research protocol, including the use of low-dose CT and pulmonary function tests, was approved by the human ethics committee of Azumi General Hospital.

Subjects

During our health-screening program for the detection of lung cancer (February 1, 2003, to January 31, 2004), enrolled individuals, who participated after lung cancer screening was publicized in our community, received a general health check including a low-dose chest CT scan and pulmonary function tests. They were also representative of the general population in that they included a highly motivated group of individuals who had some reason to worry about lung cancer. The enrolled individuals were from the general population of the Azumi or Kouhoku area around Azumi General Hospital, or belonged to an agricultural cooperative association in Nagano Prefecture. There were no selection criteria such as age, smoking history, occupation or symptoms. Low-dose chest CT scan was performed to detect lung cancer. All individuals gave their informed consent at presentation for chest CT scan and pulmonary function tests. They first underwent a low-dose chest CT and pulmonary function tests were performed. The subjects filled out a questionnaire about lifestyle, respiratory symptoms, smoking history, past histories and demographic data as of the health-screening program. The information was entered into a database. Questions about respiratory

symptoms were related to cough, sputum and shortness of breath. All of the questions had been validated previously. Questions and ratings of responses related to the above symptoms included: (1) frequency of these symptoms (none, intermittently, almost every day), (2) duration (within 1 week, within 1 month and over 3 months) and onset of these symptoms, (3) progressive or persistent symptoms. We excluded subjects with self-reported asthma, bronchiectasis, diffuse panbronchiolitis or pulmonary tuberculosis with severe obstructive pulmonary function on the basis of the clinical information, including past history and medical history, chest CT findings and self-report.

Pulmonary function tests

Pulmonary function tests were performed using our routine method.[11] All subjects performed spirometry within 15–45 min after inhaling a $\beta 2$ stimulant. The vital capacity (VC), forced vital capacity (FVC), maximal mid-expiratory flow (MMF) and FEV_1 were measured by Spiroshift SP-700 (Fukuda Denshi, Tokyo). The %MMF was calculated, and the peak expiratory flow rate (PEFR) and flow rate at 50% and 25% of the FVC (V'_{50}, V'_{25}, respectively) were calculated from the maximum expiratory flow–volume curve. Furthermore, we also calculated V'_{50}/V'_{25} and V'_{25}/height (V'_{25}/HT). VC, FEV_1 and PEFR were expressed as percentages of the predicted values (VC% predicted, FEV_1% predicted, and %PEFR, respectively) according to the prediction equations of the Japanese Society of Chest Diseases.

COPD criteria

The diagnosis of COPD was based on clinical symptoms and the results of spirometry according the criteria of the GOLD.[10] The severity of COPD was categorized according to GOLD. Five different stages were defined as follows: Stage 0 = "at risk" (presence of chronic cough and sputum production, $FEV_1/FVC \geqslant 70\%$ and $FEV_1 \geqslant 80\%$ predicted), Stage I, II, III, and IV. Those individuals reporting respiratory symptoms (intermittently/almost every day, and with a duration of over 3 months) were included in the Stage 0 group. The individuals whose symptoms of cough and sputum subsided within 1 month were classified as normal subjects. The individuals with shortness of breath were classified in the Stage 0 or COPD group.

Multislice CT

Each participant underwent a low-dose Multislice CT scan (Toshiba Asteion Multi, Tokyo, Japan) (25 mA, 120 kVp, 5-mm section thickness, 8-mm slice thickness of the reconstructions, 0.75 s of rotation, 10 mm/s table speed, and pitch of 5.5). All CT images were viewed in cine-mode format on a computer workstation by one radiologist (S.S.) and pulmonologist (K.T.) with 40 and 11 years of experience, respectively. The severity of emphysema was scored subjectively using the scoring method of Goddard on three 5-mm slices obtained at full inspiration.[12] Emphysematous destruction was identified as areas of low attenuation and hypovascular regions in the lung.[13] The percentage of the lung with emphysematous changes was determined using the following five-point scale: visual score 0, $<5\%$; 1, $5\% \leqslant \%$ low attenuation area (%LAA) $<25\%$ involvement; 2, $25\% \leqslant \%LAA < 50\%$; 3, $50\% \leqslant \%LAA < 75\%$; and 4, $\geqslant 75\%$. The maximum value was 24. A positive visual score was defined as any visual score greater than 0. The type of emphysema on chest CT findings at the three selected slices was classified as centrilobular emphysema showing mainly centrilobular emphysematous changes (CLE), paraseptal emphysema showing mainly subpleural emphysematous changes excluding bulla and bleb (PSE), panlobular emphysema showing mainly panacinar emphysematous changes (PLE), and combinations of the three types (mixed type).

Statistical analysis

We assessed the difference in sex, age, smoking history, visual score and pulmonary function variables between Stage 0 subjects. Data for continuous variables are shown as mean $\pm$ SD. We used Student's t-test to assess the differences between two groups and to test for differences in visual score and pulmonary function variables between Stage 0 and nonStage 0 subjects. Pearson's χ^2-test was performed to test for differences in the distribution of these categorical variables among each group. A stepwise method was used to test for differences in variables to adjust for multiple comparisons (SAS JMP version 5.1, SAS Institute Inc. Cary, NC). We considered P-values of less than 0.05 to be significant.

Results

As shown in Table 1, 1358 men and 888 women underwent low-dose chest CT scans and pulmonary

function tests at the Azumi General Hospital from February 1, 2003, through January 31, 2004. The subjects' mean age was 53.7±12.7 years. The numbers and percentages of male and female smokers were 1076 (79.2%), and 107 (12.0%), respectively. The numbers of never-, ex-, and present smokers were 1063, 453, and 730, respectively. The mean numbers of pack-years of ex- and present smokers were 22.7 and 30.7, respectively. Forty-eight (2.1%) of 2247 individuals (men, 40; women, 8; present smokers, 27; ex-smokers, 14; nonsmokers, 7) were diagnosed with Stage I to Stage III COPD. A total of 722 individuals had one or more respiratory symptoms, such as cough (69.8%), sputum (75.8%), or shortness of breathing (0.83%). Of the 722 subjects, 71 (9.8%) complained of chronic productive cough and sputum. They satisfied the criteria for GOLD Stage 0. There was a lower prevalence of women among both Stage 0 and normal subjects. There was a significantly higher proportion of smokers among the Stage 0 subjects than among the normal subjects ($P<0.0001$). The %MMF and %PEFR were significantly lower in Stage 0 than in normal subjects. All the listed variables, excluding %VC, were significantly worse in COPD than in Stage 0. Three patients with bronchiectasis, and six with old tuberculosis with severe obstructive pulmonary function were excluded from the study.

The chest CT of the Stage 0 group identified eight subjects with PSE, nine with CLE and two with the mixed type (Table 2). The proportion of positive visual score in the Stage 0 group was significantly higher than that in normal subjects. Sixteen of the 17 subjects with positive visual score were smokers in the Stage 0 group. The results of adjustment for multiple comparisons of each variable are shown in Tables 1 and 2, and number of pack-years, visual score and %PEFR showed significant differences between the groups.

As shown in Table 3, among normal subjects, cigarette smoking brought to the differences of airflow obstruction as results of pulmonary function tests. The proportion of positive visual score

Table 1 Characteristics and data of individuals with "Normal", "Stage 0" and "COPD".

	(A) Normal ($n=2127$)	(B) Stage 0 ($n=71$)	(C) COPD ($n=48$)	P-value (A) vs (B)
Age (years)	53.3±9.7	54.5±10.7	61.1±9.3	0.062
Sex, M/F	1262/865	56/15	40/8	0.0023
Smoking history				
No. of subjects (%)	1090 (51.2%)	52 (73.2%)	41 (85.4%)	0.0014
Current-smokers (%)	659 (31.0%)	44 (62.0%)	27 (56.3%)	<0.0001
Pack-years	29.5±16.5	37.2±22.0	38.8±17.1	0.0074
Ex-smokers (%)	431 (20.3%)	8 (11.2%)	14 (29.2%)	0.0475
Pack-years	22.1±18.1	21.4±15.3	40.9±18.6	0.061
Never-smokers (%)	1037 (48.8%)	19 (26.8%)	7 (14.6%)	0.0005
Symptoms—no. of subjects (%)				
Cough (no)	433 (20.4%)	71 (100%)	20 (41.7%)	<0.0001
Sputum (no)	476 (22.4%)	71 (100%)	25 (52.1%)	<0.0001
Pulmonary function data				
VC (L)	3.64±0.87	3.79±0.98	3.37±0.90	0.15
VC% predicted (%)	113±15	110±17	102±19	0.046
FEV_1 (L)	2.97±0.73	3.01±0.91	1.98±0.66	0.46
FVC (L)	3.58±0.85	3.62±0.99	3.10±0.89	0.48
FEV_1/FVC (%)	84.2±5.4	82.9±6.2	63.5±5.5	0.044
FEV_1% predicted (%)	111±16.2	105±19	77.5±19	0.011
V'_{25}/HT (L/s/m)	0.90±0.43	0.87±0.44	0.33±0.17	0.25
V'_{50}/V'_{25}	3.11±1.0	2.92±0.74	2.83±1.6	0.031
%MMF (%)	97.7±29	89.4±32	34.2±11	0.019
%PEFR (%)	106±23	98.2±23	70.3±22	0.011
Low-dose chest CT				
Positive visual score—no. of subjects	203 (9.5%)	19 (26.8%)	31 (64.6%)	0.0002

Data of continuous variables expressed as mean±SD and differences between groups were analyzed by ANOVA (F-test). Categorical data (sex, smoking history—number of subject, symptoms—cough, and sputum) were analyzed by χ^2-test. no, number; COPD, chronic obstructive pulmonary disease; VC, vital capacity; FVC, forced vital capacity; MMF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; V'_{50} and V'_{25}, flow rate at 50% and 25% of the forced vital capacity; V'_{25}/HT, V'_{25}/height.

Table 2 Computed tomography findings in "Normal" and "Stage 0" (excluding COPD).

	Normal ($n = 2127$)	Stage 0 ($n = 71$)	P-value
Abnormal Finding—no. of subjects (%)			
CLE	101 (4.7%)	8 (11.3%)	0.079
PSE	73 (3.4%)	9 (12.7%)	0.032
PLE	2 (0.1%)	0	>0.99
Mixed (CLE, PSE, PLE)	27 (1.3%)	2 (1.9%)	0.44
Others	165 (7.8%)	12 (17.4%)	0.0075
Positive visual score—no. of subjects	203 (9.5%)	19 (26.8%)	0.0002

*Data are mean±SD.
CLE, centrilobular emphysema; PSE, paraseptal emphysema; PLE, panlobular emphysema; COPD, chronic obstructive pulmonary disease; no, number.

Table 3 Comparison among "Normal nonsmoker", "Normal smoker" and "Stage 0" subjects.

	(A) Normal nonsmoker ($n = 1037$)	(B) Normal smoker ($n = 1090$)	(C) Stage 0 ($n = 71$)
Age (years)	54.3±9.6	52.4±9.8**	54.5±10.7
Sex, M/F	271/766	991/99**	56/15**,##
Pack-years	0	26.9±17.8	25.1±22.8
Pulmonary function data			
VC (L)	3.22±0.78	4.03±0.76**	3.79±0.98**,##
VC% predicted (%)	114±15.0	112±15.2*	110±17*
FEV_1 (L)	2.67±0.66	3.26±0.68**	3.01±0.91**,##
FVC (L)	3.14±0.75	3.91±0.77**	3.62±0.99**,##
FEV_1/FVC (%)	85.1±5.2	83.4±5.3**	82.9±6.2**
FEV_1% predicted (%)	114±16.6	108±16.4**	105±19**
V'_{25}/HT (L/s/m)	0.88±0.38	0.93±0.47**	0.87±0.44
V'_{50}/V'_{25}	3.11±1.23	3.10±0.81	2.92±0.74*,#
%MMF (%)	102±27.7	94.0±29.8**	89.4±32**,#
%PEFR (%)	105.4±22.5	105.8±23.1	98.2±23**,##
Low-dose chest CT			
Positive visual score—no. of subjects	41 (4.0%)	160 (14.7%)**	19 (26.8%)**,#

COPD, chronic obstructive pulmonary disease; VC, vital capacity; FVC, forced vital capacity; MMF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; V'_{50} and V'_{25}, flow rate at 50% and 25% of the forced vital capacity; V'_{25}/HT, V'_{25}/height; no, number.
* $P<0.05$ vs (A), ** $P<0.01$ vs (A), # $P<0.05$ vs (B), ## $P<0.01$ vs (B).

showed significant differences between normal nonsmoking and normal smoking subjects. Stage 0 subjects had the development of small airway disturbances, including V'_{25}/HT, V'_{50}/V'_{25} and %MMF compared with normal smoking subjects.

As shown in Table 4, the %MMF were significantly lower in the smoking Stage 0 than in nonsmoking Stage 0 subjects. There was a higher prevalence of men of smoking Stage 0 than that of nonsmoking Stage 0 subjects. The proportion of positive visual score of the smoking Stage 0 subjects was significantly higher than that of nonsmoking Stage 0 subjects. In Stage 0 subjects, smoking had effects on the abnormality of chest CT findings and the prevalence of men.

Discussion

There is little confirmatory data on whether Stage 0 is suitable for identifying the population at risk for the development of COPD in the general population.[14] Vestbo et al. indicated that the definition of Stage 0 enables a better spread of information as to the disease or facilitates the promotion of smoking cessation.[14] They also reported that chronic mucus hypersecretion is strongly associated with FEV_1 decline as well as subsequent hospitalization for the treatment of COPD. In subjects classified as Stage 0, productive cough in the absence of airway obstruction does not reflect increased risk, whereas chronic mucus hypersecretion with airway

Table 4 Comparison between smoking "Stage 0" and nonsmoking "Stage 0" subjects.

	(A) Stage 0 (ex-, current smokers) ($n = 52$)	(B) Stage 0 (never-smokers) ($n = 19$)	P-value (A) vs (B)
Age (years)	53.2±11.0	58.2±9.7	0.18
Sex, M/F	47/5	9/10	<0.0001
Pack-years	34.3±19.8	0	—
Pulmonary function data			
VC (L)	3.97±0.93	3.31±0.94	0.007
VC% predicted (%)	111±18.0	110±14.0	0.42
FEV_1 (L)	3.13±0.92	2.68±0.83	0.046
FVC (L)	3.77±0.97	3.23±0.96	0.027
FEV_1/FVC (%)	82.7±6.1	83.3±6.8	0.37
FEV_1% predicted (%)	105±19.0	111±17.6	0.064
V'_{25}/HT (L/s/m)	0.87±0.41	0.87±0.53	0.83
V'_{50}/V'_{25}	2.87±0.69	3.06±0.88	0.20
%MMF (%)	86.8±31.5	96.6±30.5	0.05
%PEFR (%)	99.5±25.0	94.4±17.0	0.19
Low-dose chest CT			
Positive visual score—no. of subjects	18 (34.6%)	1 (5.3%)	0.015

COPD, chronic obstructive pulmonary disease; VC, vital capacity; FVC, forced vital capacity; MMF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; V'_{50} and V'_{25}, flow rate at 50% and 25% of the forced vital capacity; V'_{25}/HT, V'_{25}/height; no, number.

obstruction does.[15] They reported that among those "at risk" in the second survey, approximately half were Stage 0 at baseline and half had experienced no symptoms. After an additional 10 years, 14% with new Stage 0 COPD and 18% with stable Stage 0 COPD had developed Stage I COPD.[14] These results do not seem to warrant a special follow-up of Stage 0 subjects to establish whether the condition is stable. Based on these results, previous studies concluded that Stage 0 is of little help in identifying subjects at risk of COPD.[14,15] However, there is little information on whether Stage 0 subjects have other abnormal pulmonary function data and abnormal chest CT findings prior to the development of airflow limitations. In the present cross-sectional study, we examined the clinical differences of Stage 0 subjects using clinical information and pulmonary function data against subjects who were subjected to low-dose CT as a health check.

The studies of Vestbo et al. indicated that cigarette smoking itself remains the best predictor of COPD development.[14,15] As shown in Table 1, the proportions of current smokers and number of pack-years of the Stage 0 group were significantly higher than those of normal subjects ($P<0.01$). Marco et al. reported that in young adults (<40 years), a considerable percentage of subjects already suffered from COPD and chronic symptoms.[16] In the present study, the V'_{50}/V'_{25}, %MMF and %PEFR of the Stage 0 subjects were significantly lower than those of the normal controls. This result suggested that subjects with chronic respiratory symptoms already suffer from airflow limitation due to small airways. The V'_{50}/V'_{25} and %MMF is associated with the small airway disturbance induced by cigarette smoking. There are Stage 0 subjects with a history of smoking and abnormal pulmonary function data showing small airway disturbances, including the %MMF and %PEFR, among those classified as Stage 0. However, the %MMF and %PEFR values of the Stage 0 subjects were significantly higher than those with COPD, probably due to the development of pulmonary damage in the latter group. Jackson et al. reported that a cut-off %PEFR value of less than 80% allows the detection of more than 90% of people with COPD.[17] Moreover, cigarette smoking only showed a significant difference between smoking and non-smoking Stage 0 subjects based on the results of multiple comparisons. Therefore, Stage 0 subjects with abnormal pulmonary function data may represent a group at higher risk, and thus it is important to detect the smoking Stage 0 among Stage 0 and normal subjects.

Chest CT findings can show the emphysematous changes with reference to smoking history and FEV_1%. Chest CT has been reported to accurately reflect the histological structure of the lung and to be useful in the diagnosis and evaluation of various types of pulmonary parenchymal diseases.[10] Several studies designed to detect and quantify