noma, the corresponding proportions were 3% (4/156) and 11% (12/113), respectively. The degree of aggressiveness of the women's cancers thus tended to be slightly lower than that of the men's. But if in 10% of the women's cases the growth rate was, for example, one half of that in the men's cases, this would have made the prevalence OR (incidence density) no higher than 1.1. Table 5 clearly indicates that insofar as a given level of smoking causes lung cancer more commonly in women than in men, the excess cases are principally adenocarcinomas, as has been shown in other studies.[9,13-15]

The hypothesis that women may be more susceptible to tobacco carcinogens is biologically plausible.[32,33] While evidence from some epidemiological cohort studies does not substantiate this idea,[10-12] a subsequent study based on the national SEER registry[9] again suggested the increased susceptibility of women. If additional studies add supporting evidence, the notion of women's susceptibility to tobacco carcinogens warrants serious consideration.

If lung cancer risk for women who smoke is indeed higher than the risk for men of the same age who smoke, as indicated by the evidence presented here, this suggests that antismoking efforts directed toward girls and women need to be even more serious than those directed toward boys and men. In the same vein, insofar as screening for lung cancer is practiced among smokers, female sex calls for screening at lower levels of smoking history than the corresponding indication threshold in men. Specifically, if men of a given age are to be screened if the number of pack-years of past smoking is at least X, the regression analysis of the 2 screening series combined suggests that the corresponding threshold for women would be X–0.662/0.0138=X–48 pack-years, where 0.662 and 0.0138 are the fitted coefficients of the indicator of female sex and pack-years of smoking; that is, that the screening threshold for women of a given age should be 50 pack-years lower than that for men of the same age.

Table 5. Cell Type Distribution of the Diagnosed Cases of Lung Cancer

Cell Type	No. (%) Women (n = 156)	Men (n = 113)	Total (N=269)
Carcinoid, typical	6 (4)	1 (1)	7 (3)
Adenocarcinoma (bronchioloalveolar)	3 (2)	4 (4)	7 (3)
Adenocarcinoma (other)	111 (71)	63 (56)	174 (64)
Squamous cell carcinoma	22 (14)	19 (17)	41 (15)
Non–small cell carcinoma, NOS	3 (2)	6 (5)	9 (3)
Carcinoid, atypical	2 (1)	0	2 (1)
Large cell carcinoma	5 (3)	4 (3)	9 (3)
Small cell carcinoma	4 (3)	12 (11)	16 (6)
Other	0	4 (3)	4 (2)

Abbreviation: NOS, not otherwise specified.

Table 6. Multivariate Cox Regression Analysis of 269 Baseline Diagnosed Cases of Lung Cancer for the Hazard Ratio of Fatal Outcome, Women vs Men by Controlled Covariates*

Covariates	Coefficient (SE)*	Hazard Ratio (95%CI) Estimate	*P* Value†
None	−1.12 (0.31)	0.33 (0.18-0.61)	<.001
Smoking, stage, cell type, and resection	−0.75 (0.32)	0.48 (0.25 0.89)	.02

Abbreviation: CI, confidence interal.
*Coefficient of sex indicator: 1 if female, 0 otherwise.
†Two-sided.

It is well-established by the evidence accumulated over the past 20 years that women with lung cancer survive the disease better than men,[9,12-20] and that this difference is more pronounced when the cancer is diagnosed at an early stage.[18-20] Cancer stage at diagnosis, cell type, or treatment do not appear to be entirely explanatory of this difference.[21] As 85% (229/269) of the cases considered here were clinical stage I at diagnosis, the fatality hazard ratio in favor of women, conditional for pack-years of smoking, disease stage, tumor cell type, and resection was more pronounced than those reported by others.[21] Despite the conditionality, it is not clear whether this survival difference is because lung cancer in women tends to be more commonly curable or less malignant. If lung cancer is more commonly curable in women, then the need to screen women at a lower threshold than men is warranted. If lung cancer is less malignant in women, there may be less need to screen women at a lower threshold.

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Survival of Patients with Stage I Lung Cancer Detected on CT Screening

The International Early Lung Cancer Action Program Investigators*

ABSTRACT

BACKGROUND

The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.

METHODS

In a large collaborative study, we screened 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005, 27,456 repeated screenings were performed 7 to 18 months after the previous screening. We estimated the 10-year lung-cancer–specific survival rate among participants with clinical stage I lung cancer that was detected on CT screening and diagnosed by biopsy, regardless of the type of treatment received, and among those who underwent surgical resection of clinical stage I cancer within 1 month. A pathology panel reviewed the surgical specimens obtained from participants who underwent resection.

RESULTS

Screening resulted in a diagnosis of lung cancer in 484 participants. Of these participants, 412 (85%) had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% in this subgroup (95% confidence interval [CI], 84 to 91). Among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the survival rate was 92% (95% CI, 88 to 95). The 8 participants with clinical stage I cancer who did not receive treatment died within 5 years after diagnosis.

CONCLUSIONS

Annual spiral CT screening can detect lung cancer that is curable.

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IN 1993, THE EARLY LUNG CANCER ACTION Project (ELCAP) initiated a study of the early diagnosis of lung cancer in cigarette smokers with the use of annual screening with spiral computed tomography (CT).[1,2] The principal finding was that more than 80% of persons given a diagnosis of lung cancer as a result of annual CT screening had clinical stage I cancer.[3] This result has been confirmed by others[4] who have adopted the updated protocol.[5,6] The question remains, however, whether early intervention in such patients is sufficiently effective to justify screening large asymptomatic populations who are at risk for lung cancer.[7,8] We report the results of all patients in the study with stage I lung cancer detected with the use of spiral CT screening, including those who underwent surgical resection.

METHODS

Screening was defined according to the International ELCAP (I-ELCAP) protocol[6] so that data from participating institutions could be pooled. Each institution was required to document the initiation of screening in each participant and all subsequent screenings of that participant for as long as the screening continued, transmit the data and images to the coordinating center at Weill Medical College of Cornell University by means of the study's Web-based management system for CT screening for lung cancer,[9] submit pathological specimens to the coordinating center, and follow quality-assurance procedures specified by the protocol. All participants gave written informed consent, and the institutional review board at each participating institution approved the protocols (Fig. 1).

The protocol specified a common regimen of screening but allowed each participating institution to specify its criteria for enrollment. The regimen included the technical variables for the initial low-dose spiral CT scan, which were the same for the baseline and annual screenings. However, the definition of a positive result on the initial CT scan and the diagnostic workup leading to a diagnosis of lung cancer were different for the baseline screening and annual screening.

For baseline screening, a positive result on the initial low-dose CT scan was defined as the identification of at least one solid or partly solid noncalcified pulmonary nodule 5 mm or more in diameter, at least one nonsolid noncalcified pulmonary nodule 8 mm or more in diameter, or a solid endobronchial nodule.[10] If none of the noncalcified nodules identified met the study criteria for a positive result or if the test was negative, CT was repeated 12 months later. The diameter of the nodule was defined as the average of the length and width of the cross-sectional area of the largest nodule in the CT images. The consistency of the nodule was defined as solid if the nodule obscured the entire lung parenchyma, partly solid if it obscured part of the lung parenchyma, and nonsolid if it obscured none of the parenchyma.[11] If the result was positive, the type of workup depended on the diameter of the largest nodule. For nodules 5 to 14 mm in diameter, the preferred option was to perform another CT at 3 months; if the images showed growth of the nodule,[12] then biopsy, ideally by fine-needle aspiration, was to be performed, whereas if there was no growth, the workup was stopped. The other option was to perform positron-emission tomography (PET) immediately, and if the results were positive, biopsy was to be performed; otherwise, CT was to be performed at 3 months. For nodules 15 mm in diameter or larger (whether solid, partly solid, or nonsolid), immediate biopsy was an option in addition to the options already specified for smaller nodules. When infection was suspected, a 2-week course of antibiotics followed 1 month later by CT was an alternative to all the options mentioned,[13] and if no resolution or growth was observed, biopsy was to be performed; otherwise, the workup was stopped. For all participants for whom the workup was stopped or for whom the biopsy did not lead to a diagnosis of lung cancer, CT was to be repeated 12 months after the baseline CT.

For annual screenings, a positive result was considered to be any newly identified noncalcified nodule, regardless of size. If no new nodule was identified, CT was to be repeated 12 months later. If one or more new nodules were identified, the workup depended on the diameter of the largest nodule. If all nodules were less than 3.0 mm in diameter, or if the largest nodule was more than 3.0 mm but less than 5.0 mm in diameter, CT 6 or 3 months later, respectively, was to be performed. If no growth was seen in any of the nodules, the workup was stopped. If at least one of the noncalcified nodules was 5.0 mm or larger in diameter, then an immediate 2-week course of a broad-spectrum antibiotic was prescribed, followed 1 month later by CT. If the nodules showed no

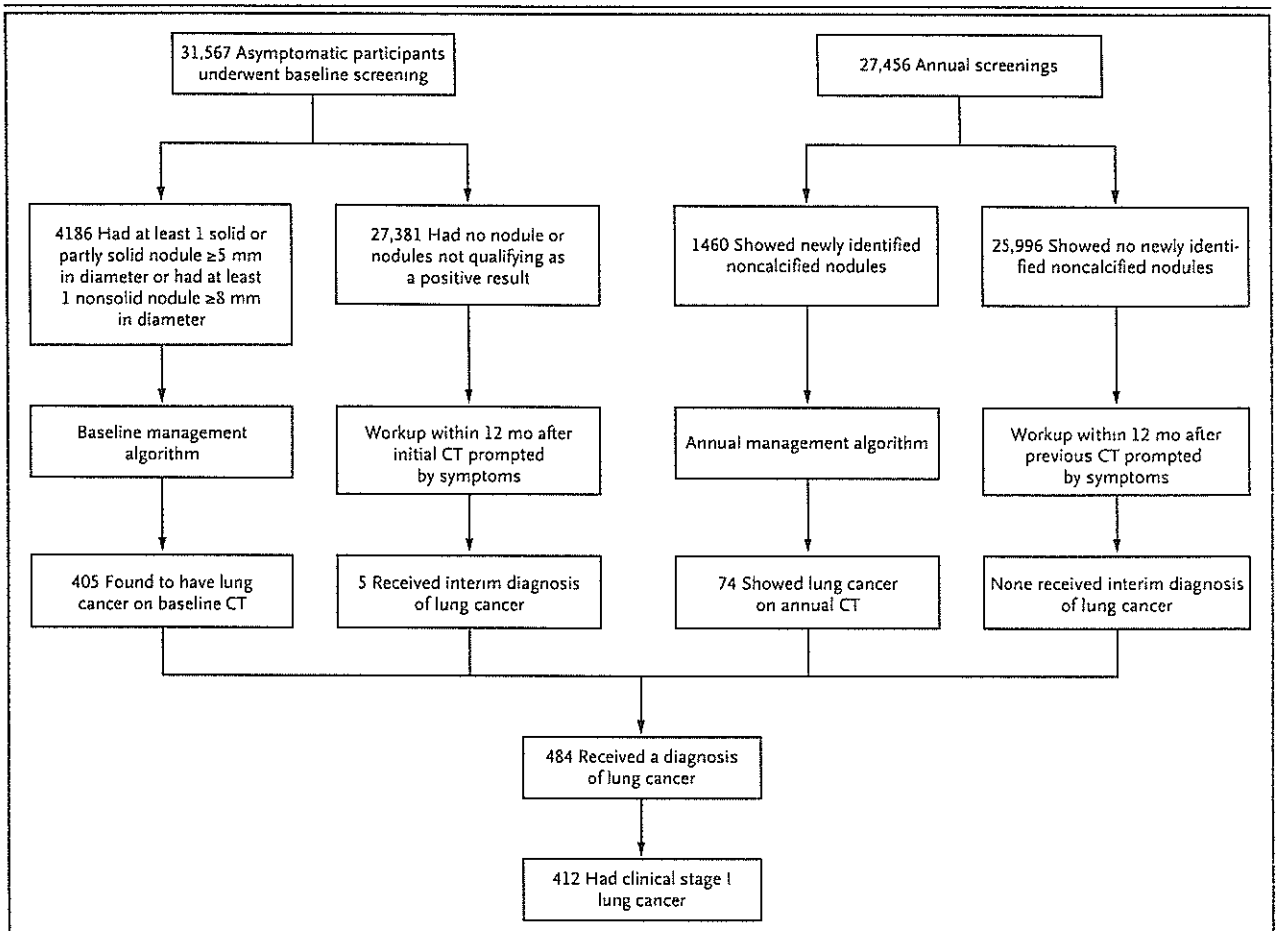

Figure 1. Diagnoses of Lung Cancer Resulting from Baseline Screening and Annual Screening with CT.

A description of the I-ELCAP management algorithm for baseline CT and repeated CT screening is available in the study protocol.[6]

resolution or growth, biopsy was to be performed; otherwise, the workup was stopped. PET was an alternative to immediate biopsy; if the result was positive, biopsy was to follow. If the result was indeterminate or negative, CT was to be performed 3 months later, and if the scans showed growth, biopsy was to follow. Otherwise, the workup was stopped. For all patients for whom the workup was stopped or when biopsy did not result in a diagnosis of lung cancer, CT was to be repeated 12 months after the previous annual CT.

The protocol provided recommendations for the diagnostic workup in participants with a positive result on CT, with the decision regarding how to proceed left to each participant and the referring physician. The I-ELCAP protocol did not require that its recommendations for the workup of a nodule be followed, but it did require a firmly established final diagnosis of lung cancer and documentation of the workup in the management system. After the diagnosis of lung cancer was established, the type of intervention, if any, was left to the discretion of the participant and the physician. Documentation in the management system of the timing and type of intervention, if any, and follow-up with respect to manifestations of spread or death up to 10 years after diagnosis, were required.

A total of 31,567 asymptomatic men and women underwent baseline screening between 1993 and 2005 (median, 2001). The participants, who were 40 years of age and older, were at risk for lung cancer because of a history of cigarette smoking, occupational exposure (to asbestos, beryllium, uranium, or radon), or exposure to secondhand smoke without having smoked themselves; in Azumi, Japan, they participated as part of the annual health screening program (Table 1). All partici-

Table 1. I-ELCAP Participants, According to the Smoking Status, Exposure to Secondhand Smoke, and Occupational Exposures.

Program	Participants (N=31,567)
	no. (%)
Azumi Health Care Program in Japan	
Current or former smokers	3,087 (10)
Persons who had never smoked with exposure to secondhand smoke	3,299 (10)
Programs in the United States, Europe, Israel, and China	
Current or former smokers	23,052 (73)
Persons who had never smoked	
Occupational exposure*	1,690 (5)
Exposure to secondhand smoke with or without family history of lung cancer	439 (1)

* This category includes exposure to asbestos, beryllium, uranium, or radon.

pants were considered fit to undergo thoracic surgery. A total of 27,456 annual screenings were conducted between 1994 and 2005 (median, 2002), each of which was performed 7 to 18 months after the previous screening. At baseline, the median age of the participants was 61 years (range, 40 to 85), and the median number of pack-years of smoking was 30 (range, 0 to 141); on annual CT, the median values were an age of 62 years (range, 41 to 86) and 35 pack-years (range, 0 to 141). Among the participants, 13% (4186 of 31,567) who underwent baseline CT and 5% (1460 of 27,456) who underwent annual CT had a positive result that required immediate further workup. A biopsy of a pulmonary nodule as recommended in the protocol was performed in 535 of the participants with a positive result on the baseline or annual CT and led to a diagnosis of malignant disease in 492 of the participants (lung cancer was diagnosed in 479 and lymphoma or metastases from cancers other than lung cancer in 13) and no evidence of malignant disease in 43. The diagnosis was classified as having been identified during baseline screening when the nodule was first identified on the baseline CT, even for cases not meeting the criteria for a positive result, regardless of when the diagnosis was made. When the nodule was first identified on an annual CT, it was attributed to the annual screening. If the result on the baseline or annual CT was negative and a diagnostic workup was subsequently prompted by suggestive symptoms (or incidental findings) before the next scheduled annual CT, the finding was classified as an interim diagnosis. To fully document interim diagnoses of lung cancer, the protocol required that each enrolled participant who had not returned for the next scheduled screening be contacted 1 year after the previous screening. If contact could not be made either directly or through relatives of the participant, the referring physician was contacted to ascertain whether a diagnosis of lung cancer had been made.

We determined the distribution of the baseline and annual screenings and the resulting diagnoses according to age and median pack-years of cigarette smoking (Table 2). Each diagnosis of lung cancer was classified according to clinical stage with the use of standard criteria based on the clinical examination and the results of imaging.[14] The presence or absence of lymph-node (N) and distant metastases (M) was assessed on the most recent CT obtained before diagnosis and from PET (performed in 166 of the 484 participants who received a diagnosis of lung cancer). The cancer was classified as N0M0 if on CT the widths of all mediastinal lymph nodes were less than 10 mm and no hilar lymph nodes or distant metastases were identified (and PET, if performed, showed no abnormal uptake). For the purpose of this study, stage I cancers included those classified as N0M0 with more than 1 adenocarcinoma so long as all adenocarcinomas were 30 mm or less in diameter.[6]

The specimens obtained from participants who underwent surgical resection were examined at each institution according to the I-ELCAP pathology protocol,[15] which specified the preparation of the specimen and the findings that were to be documented by the pathologist at the hospital where the resection was performed. The protocol also specified the review process: a five-member pathology-review panel consisting of expert pulmonary pathologists was to reach a consensus diagnosis for each case of cancer and identify lymph-node involvement, additional cancers, and pleural, lymphatic, vascular, bronchial, and basement-membrane invasion by the cancer. For 22 of the 411 participants who underwent resection (5%), specimens could not be obtained from a nonparticipating hospital, and the panel therefore reviewed the detailed surgical and pathological reports for the relevant information.

All patients given a diagnosis of lung cancer were followed annually by the principal investigator and by the study coordinator at each participating institution, who submitted the information

Table 2. Frequency Distribution of Lung-Cancer Diagnoses on Baseline and Annual CT Screening, According to Age and Median Pack-Years of Cigarette Smoking.

Age	Baseline Screening			Annual Screening		
	Smoking History	No. Screened	Diagnosis of Lung Cancer	Smoking History	No. Screened	Diagnosis of Lung Cancer
	median pack-yr		*no. (%)*	*median pack-yr*		*no. (%)*
40–49 yr	15	4,066	8 (<1)	20	1,324	1 (<1)
50–59 yr	28	9,948	67 (1)	30	6,678	7 (<1)
60–69 yr	38	12,184	206 (2)	40	11,879	29 (<1)
70–79 yr	38	4,840	116 (2)	40	6,692	33 (<1)
80–86 yr	30	529	13 (2)	37	883	4 (<1)
Total	30	31,567	410 (1)*	35	27,456	74 (<1)

* The number includes five participants with interim diagnoses.

required by the protocol to the coordinating center. When a participant was known to have died, the date and cause were obtained from the participant's physician, family members, or both. Death resulting from treatment was considered to have been caused by lung cancer. Follow-up from diagnosis to death from lung cancer, the last contact, or May 30, 2006, whichever came first, was documented for each participant. The duration of follow-up ranged from 1 to 123 months (median, 40).

Kaplan–Meier curves were calculated for lung-cancer–specific survival as of the date of diagnosis, irrespective of the type of treatment, including no treatment, for all participants with lung cancer, irrespective of the stage of the cancer, and for the subgroup with clinical stage I cancer. Survival curves were also calculated for participants who underwent resection of clinical stage I cancer within 1 month after diagnosis and those who did not receive treatment. On the basis of these curves, we estimated the 10-year survival rates. The curves were constructed with the use of SAS statistical software (version 8), which also produced the standard error for the estimates.

RESULTS

Baseline screening of 31,567 asymptomatic persons who were at risk for lung cancer and annual screening of 27,456 resulted in the diagnosis of lung cancer in 405 and 74 participants, respectively (Fig. 1). Another five participants received interim diagnoses of lung cancer that were prompted by the development of symptoms within 12 months after the baseline screening. Of these 484 participants given a diagnosis of lung cancer, 411 underwent resection; 57 received radiation, chemotherapy, or both; and 16 received no treatment. Because survival rates among the participants who underwent baseline screening and those who underwent annual screening did not differ significantly, Kaplan–Meier estimates of lung-cancer–specific survival were calculated for all 484 participants (Fig. 2). The estimated 10-year survival rate for all participants, regardless of tumor stage and treatment, was 80% (95% confidence interval [CI], 74 to 85); as of May 2006, 75 of the 484 participants had died of lung cancer, including 2 who died within 4 weeks after surgery, yielding an operative mortality rate of 0.5% (2 of 411 participants).

Of the 484 participants who received a diagnosis of lung cancer, 412 (85%) had clinical stage I lung cancer. In this subgroup, the estimated 10-year survival rate regardless of treatment was 88% (95% CI, 84 to 91); as of May 2006, 39 of these 412 patients had died of lung cancer. Of these 412 participants, 375 had undergone surgical resection (284 lobectomy, 60 wedge resection, 21 segmentectomy, and 10 bilobectomy); 29 did not undergo resection but received chemotherapy, radiation, or both; and the remaining 8 did not receive treatment. Figure 2 also shows the lung-cancer–specific survival rate among the 302 participants who underwent resection within 1 month after diagnosis, among whom the estimated 10-year survival rate was 92% (95% CI, 88 to 95). All eight untreated patients died within 5 years after diagnosis.

Among the 412 participants with clinical

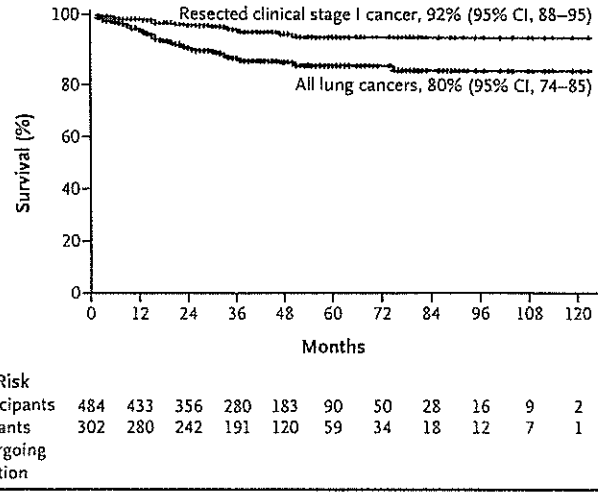

Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

Table 3. Types of Cancer among 412 Participants with Clinical Stage I Lung Cancer Detected on Baseline or Annual CT Screening.

Type of Cancer	Diagnosed on Baseline Screening (N=348)	Diagnosed on Annual Screening (N=64)
	no. of participants	
Adenocarcinoma		
Bronchioloalveolar subtype	20	1
Other subtypes	243	30
Squamous cell	45	14
Adenosquamous	3	0
Non–small-cell*	5	2
Neuroendocrine		
Atypical carcinoid	2	1
Large cell	15	8
Small cell	9	7
Other	6	1

* If this cell type cannot be differentiated, the category is known as "not otherwise specified."

stage I cancer, the distribution according to the type of cell is shown in Table 3. The median tumor diameter was 13 mm at baseline and 9 mm on annual CT. The pathology-review panel confirmed the diagnosis of clinical stage I cancer in the specimens obtained from the 375 participants who underwent resection according to World Health Organization criteria of 2004.[16] With regard to spread or invasion (Table 4), the panel identified lymph-node metastases (hilar or ipsilateral mediastinal) in 28 participants (7%) and more than one cancer, either in the same or in different lobes, in another 35 (9%). Among the remaining participants, each with a solitary cancer, the panel identified invasion of the pleura in 62 (17%); bronchial, vascular, or lymphatic invasion or a combination in another 28 (7%); invasion of the basement membrane alone in 203 (54%), and no invasion in the remaining 19 (5%). (Because of rounding, percentages may not total 100.) Thus, of the 375 participants who underwent resection, 347 had pathological stage I cancer, and their estimated 10-year survival rate was 94% (95% CI, 91 to 97).

DISCUSSION

In making decisions about instituting CT screening for lung cancer, a major consideration is the outcome of treating a cancer detected on screening. In our study, the estimated 10-year lung-cancer–specific survival rate among the 484 participants with disease diagnosed on CT, regardless of the stage at diagnosis or type of treatment (including no treatment), was 80% (95% CI, 74 to 85) (Fig. 2). Among the 412 participants with clinical stage I lung cancer — the only stage at which cure by surgery is highly likely — the estimated 10-year survival rate was 88% (95% CI, 84 to 91), and among those with clinical stage I lung cancer who underwent surgical resection within 1 month after the diagnosis, the rate was 92% (95% CI, 88 to 95). The diagnosis of lung cancer of one type or another was verified by a panel of five expert pulmonary pathologists. In our series, the operative mortality rate was low — 0.5% — and was less than the 1.0% reported with lobectomy in a large cooperative study.[17]

Sobue et al.[18] reported a 5-year survival rate of 100% in their series of 29 patients who underwent resection after pathological stage I cancer was detected on CT. Before CT screening, reports based on registries showed 10-year survival rates of 80% among 17 patients with pathological stage I lung cancer 20 mm or less in diameter[19] and 93% among 35 patients with pathological stage I cancer less than 10 mm in diameter.[20] The National Cancer Institute's Surveillance, Epidemiology, and End

Table 4. Extent of Spread of Cancer in 375 Participants Who Underwent Resection of Clinical Stage I Lung Cancer According to Whether Cancer was Detected on Baseline or Annual CT Screening.

Extent of Spread	Diagnosed on Baseline Screening (N=320)	Diagnosed on Annual Screening (N=55)
	no. of participants	
Metastases to lymph nodes	22	6
No metastases to lymph nodes		
More than 1 cancer	29	6
Solitary cancer with invasion		
Pleural invasion	51	11
No pleural invasion but lymphatic, vascular, or bronchial spread (or a combination)	24	4
Basement membrane only	175	28
Solitary cancer without invasion	19	0

Results (SEER) registry, the largest U.S. cancer registry, reported an 8-year survival rate of 75% among patients with pathological stage I cancer with nodules less than 15 mm in diameter who had undergone resection.[8] Although the lung cancers in these three series were not detected on CT screening, most were presumably incidentally detected on imaging performed for other reasons in people who had no symptoms of lung cancer.

CT screening according to the I-ELCAP regimen can detect clinical stage I lung cancer in a high proportion of persons when it is curable by surgery. In a population at risk for lung cancer, such screening could prevent some 80% of deaths from lung cancer. In comparison, in the United States at present, annually approximately 173,000 persons are diagnosed with lung cancer and 164,000 deaths are attributed to this disease,[21] so that approximately 95% of those who are diagnosed with lung cancer die from it.

Are these results sufficiently effective to justify screening people who are at risk of lung cancer? As compared with mammographic screening for breast cancer, for lung cancer the rates of detection among the participants in this study who were 40 years of age and older were 1.3% on baseline CT screening and 0.3% on annual screening (Table 2), values that were slightly higher than those for the detection of breast cancer (0.6 to 1.0% on baseline screening) and similar to those for annual screening (0.2 to 0.4%) among women 40 years of age and older.[22] The rate of cancer detection depends on the risk profile of those undergoing screening; the higher the risk, the more productive the screening. Thus, as expected, CT screening of the original participants in ELCAP, who were former and current smokers 60 years of age and older,[1,2] was more productive in detecting lung cancer (detection rates, 2.7% on baseline screening and 0.6% on annual screening) than among participants in the expanded study. The cost of low-dose CT is below $200,[23-26] and surgery for stage I lung cancer is less than half the cost of late-stage treatment.[26,27] Using the original ELCAP data and the actual hospital costs for the workup, we found CT screening for lung cancer to be highly cost-effective.[23] Other estimates of the cost-effectiveness of CT screening for lung cancer for various risk profiles[24-26,28] are similar to that for mammography screening.[29,30]

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APPENDIX

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Improving Radiologists' Recommendations With Computer-Aided Diagnosis for Management of Small Nodules Detected by CT[1]

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Rationale and Objectives. To evaluate how computer-aided diagnosis (CAD) can improve radiologists' recommendations for management of possible early lung cancers on CT.

Materials and Methods. Twenty-eight lung cancers and 28 benign lesions were employed. Each group of 28 lesions was classified into subgroups of two sizes (9 between 6 and 10 mm and 19 between 11 and 20 mm) and three patterns (8 with pure ground glass opacity [GGO], 12 with mixed GGO and 8 solid lesions). Sixteen radiologists participated in the observer study, first without and then with CAD. Radiologists' recommendations, including (1) follow-up in 12 months, (2) in 6 months, (3) in 3 months, or (4) biopsy, were compared at three levels of their malignancy probability ratings (low: 1%–33%; medium: 34%–66%; high: 67%–99%) for 896 observations (56 lesions by the 16 radiologists) in the two size subgroups and three patterns.

Results. The number of recommendations changed by radiologists by use of CAD was 163 (18%) among all 896 observations. Among these changed recommendations, the fraction showing a beneficial effect from CAD was 68% (111/163), and the fraction showing a beneficial effect regarding biopsy recommendations was 69% (48/70). With CAD, the radiologists' performance regarding biopsy recommendations was significantly improved for 43 lung cancers (31 changed to biopsy versus 12 changed away from biopsy; $P = .003$) and was also improved for 27 benign lesions (10 changed to biopsy versus 17 changed away from biopsy; $P = .18$). Most of the cancers with improved recommendations were solid lesions or mixed GGO and relatively large.

Conclusion. CAD has the potential to improve the appropriateness of radiologists' recommendations for small malignant and benign lesions on CT scans.

Key Words. Lung neoplasms, CT; Computer diagnostic aid; Lung, module.

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Among diagnostic imaging modalities, computed tomography (CT) has the highest sensitivity for detection of small pulmonary lesions. However, it is difficult for radiologists to correctly distinguish cancers from noncancerous lesions (false positives) and to make appropriate and consistent recommendations management of patients with suspicious lesions. On the one hand, a large number of false positives will lead to unnecessary patient anxiety and will increase the increased economic costs and radiation exposure. A high rate of false positives can also lead to unnecessary investigation such as CT scans, biopsy, and even surgery. On the other hand, in the case of lung cancers (true positives), if radiologists fail to make an appropriate recommendation such as biopsy or surgery, the patients may miss an opportunity for cure.

The Food and Drug Administration has approved the clinical use of some computer-aided diagnosis (CAD) detection systems in screening for clinical use, especially for breast cancer screening on mammography in the United States. Gur et al (1) reported that the introduction of detection CAD into a large clinical practice (115,571 screening mammograms) was not associated with statically significant changes in both recall and breast cancer detection rates. Commercially available detection CAD systems show marks, including true positives (cancers) and false positives (noncancerous lesions also anatomic structures), on each whole image (1–3). Recently, automatic classification CAD schemes for distinction of malignant and benign lesions have been developed in some universities (4–8) that show an estimated likelihood of malignancy for each segmented lesion based on its image features. Some observer studies using mammograms reported that classification CAD had a beneficial effect for radiologists' diagnostic accuracy for classifying malignant and benign breast masses and their recommendations regarding biopsy (5,6).

It is important that a larger database, including large number of lesions and a variety of lesion patterns, be used for developing classification CAD. The thin-section CT database for developing our classification CAD scheme used in this study comprised follow-up exams obtained from a 3-year CT lung cancer screening program (17,892 examinations). The database included 61 primary lung cancers (size range 6–19 mm; mean 12 mm) and 183 benign nodules (size range 3–20 mm; mean 7 mm) with three different patterns (8,9). We have reported (8) that our CAD scheme has the potential to improve radiologists' diagnostic accuracy for lesion classification and also to improve radiologists' recommendations in an observer study. The data analysis in the previous report (8) was independently calculated for 16 observers, and the radiologists' recommendations were improved by increasing the number of biopsy recommendations for actual early cancers (statistically significant) and by reducing the number for actual benign ones (not significant) in an observer study. The current study used the same data from the same observer test as used previously (8). Our purpose in this study was to evaluate further how CAD can assist radiologists in their recommendation management of possible early lung cancers that have different sizes and patterns.

MATERIALS AND METHODS

Institutional review board approval and informed observer consent were obtained.

Database

Our database was obtained as part of an annual 3-year CT screening for lung cancer in a general population in Nagano, Japan (8,9), which included 59 patients (27 men, 32 women, mean age 64.6 years) with 61 primary small lung cancers (mean size 12.3 mm; size range 6–20 mm; 18 nodules with pure ground glass opacity [GGO]; 28 with mixed GGO; and 15 with solid opacity), and 169 patients (99 men, 70 women, mean age 61.6 years) with 183 benign lesions (mean size 7.2 mm; size range 3–20 mm; 12 with pure GGO, 30 with mixed GGO, and 141 with solid opacity). All patients gave informed consent. All cancers were confirmed by surgery, and benign lesions were confirmed by surgery or follow-up (resolved or no change for 2 years or more). The mean size (average length and width) of each nodule was recorded by one radiologist (F.L.). The three types of patterns of these lesions, including pure GGO, mixed GGO, and solid opacity, were viewed independently and grouped by three radiologists (F.L. among them) without knowledge of the final diagnosis, and then a consensus was reached through discussion. Thin-section CT scans were performed on a helical scanner (CT HiSpeed Advantage, GE, Milwaukee, WI) with a standard tube current (200 mA) to cover the entire lesion, with 1-mm collimation and a bone reconstruction algorithm with a 0.5-mm interval.

CAD

With our CAD scheme, the nodules were segmented automatically by use a dynamic programming technique.

The technique has been described in detail elsewhere (7). A total of 41 and 15 image features based on two-dimensional and three-dimensional volume data, respectively, were determined from quantitative analysis of the nodule outline and pixel values. Linear discriminant analysis was employed for distinguishing benign from malignant nodules. The performance of this CAD scheme was evaluated based on a "leave-one-out" testing method by use of 61 malignant and 183 benign nodules. For the input of the linear discriminant analysis, we selected many combinations from 56 features and two clinical parameters (age and gender). The final features included effective diameter, contrast, margin or edge, shape, attenuation, and internal homogeneity of the segmented nodules.

Our computerized classification method outputs a percentage (1%–99%) indicating the likelihood of malignancy. The performance of the classification scheme yielded an A_z value of 0.937 (0.934 for lesions at 6–10 mm, 0.855 for lesions at 11–20 mm, 0.919 for nodules with pure GGO, 0.852 for nodules with mixed GGO, and 0.957 for solid nodules) for distinction between 61 lung cancers and 183 benign nodules.

Case Selection

Twenty-eight patients (mean age 63.4 years; 14 men and 14 women) with lung cancers and 28 patients (mean age 64.2 years; 17 men and 11 women) with benign lesions on thin-section CT were included in this observer study. The 28 malignant lesions were randomly selected from 61 lung cancers, and the 28 benign lesions were selected by matching of their size and pattern to the cancers from 183 benign lesions among our database. For both cancers and benign lesions, 9 lesions were in the range of 6–10 mm and 19 lesions in the range of 11–20 mm; the lesion patterns were 8 pure GGO, 12 mixed GGO, and 8 solid opacity. The performance of the classification scheme yielded an A_z value of 0.831 (0.842 for lesions at 6–10 mm, 0.870 for lesions at 11–20 mm, 0.910 for nodules with pure GGO, 0.814 for nodules with mixed GGO, and 0.783 for solid nodules) for the 28 lung cancers and 28 benign nodules. The 56 lesions used in this observer study were the largest number of lesions that could be matched in size and pattern between the 183 benign lesions and the 61 lung cancers in our database.

The 28 cancers included 19 well-differentiated adenocarcinomas, 5 other adenocarcinomas, 2 squamous cell carcinomas, and 2 localized small-cell carcinomas. Among the 28 benign lesions, 2 (inflammatory pseudotumor and sclerosing hemangioma) were confirmed by surgery, 19 had resolved on follow-up examination, and 7 had not changed for 2 years or more.

Observer Study

Sixteen radiologists (H.M. among them) participated in this observer study. The 16 radiologists, including 7 chest radiologists and 9 general radiologists, have a mean of 14 years of experience (range 7–26 years). Consecutive region of interest images for each lesion on thin-section CT were presented for interpretation by use of a cine-type display on a high-resolution CRT monitor. The windowing was initially set at a width of 1500 Hounsfield units and a level of −550 Hounsfield units, but could be adjusted by the observer. In addition, zooming capability was provided. Two clinical parameters (age and gender) were provided to the observers on the monitor.

It was explained to the observers that the purpose of this study was to assist radiologists in distinguishing benign from malignant lesions on thin-section CT by use of a CAD scheme. The observers were informed that the lesions used in this study were obtained from an annual 3-year CT screening for lung cancer in a general population in Japan. The instructions for the observers included (a) the role of CAD output as a "second opinion;" (b) 28 malignant (6–10 mm: 9 cases; 11–20 mm: 19 cases; and pure GGO: 8 cases, mixed GGO: 12 cases, and solid opacity: 8 cases) and 28 benign lesions (matched to the cancers in size and pattern) are included in this study; (c) the sensitivity and specificity of our CAD scheme, for a threshold of 50% likelihood of malignancy, are 80% and 75%, respectively; (d) click on a bar (left: benignancy, right: malignancy) on the screen by using a mouse to indicate your confidence level regarding the likelihood of malignancy (from 1% to 99%) of a lesion first without and then with computer output; and (e) after indicating your confidence (without and with CAD), click on one of four recommendations: (1) return to annual screening, in 12 months; (2) follow-up in 6 months; (3) follow-up in 3 months; or (4) biopsy/surgery.

For a training session before the test, we provided five different cases so that the observers could learn how to operate the cine mode interface and how to take into account the computer output in their decision. There was no pretest training regarding interpretative guidelines for recommendations to radiologists. Radiologists' recommendations without and with CAD were freely decided by each of the observers in this observer study. The reading time was not limited. The average reading time for 56 test

cases by 16 radiologists was 46 minutes (range 28–100 minutes; 0.82 minute per case).

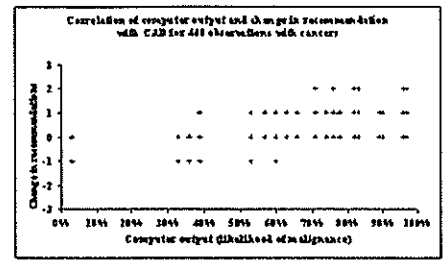
Data Analysis

The radiologists' recommendations without and with CAD were analyzed for 896 observations (56 lesions by the 16 radiologists) and were compared at three levels of malignancy (low: 1%–33%; medium: 34%–66%; and high: 67%–99%) for malignant and benign lesions. The test for proportion was used for comparison of the difference in changes on recommendations between those having a beneficial and those have a detrimental effect from CAD for malignant and benign lesions. A chi-square test for independence was used for comparison of the difference in the proportions between radiologists' biopsy recommendations without and with CAD. The recommendations were further classified as "biopsy" and "other" for highly suspicious lesions for which the radiologists indicated their confidence ratings to be 67%–99%. The chi-square test (including a multiple-group test) was used independently for comparison of the difference between (1) lesion sizes (lesions at 6–10 mm and those at 11–20 mm) and (2) lesion patterns (pure GGO, mixed GGO, and solid opacity) for biopsy recommendations on these highly suspicious lesions, without and with CAD.

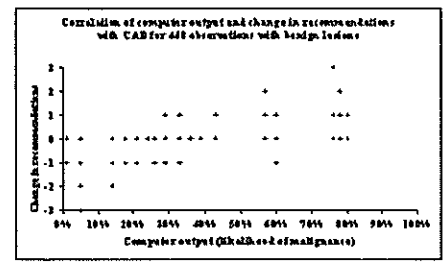
RESULTS

Figure 1 shows the correlation between computer output and change in the 16 radiologists' recommendations for 896 observations. With CAD, the fraction by which the radiologists changed their recommendations was 18% (163/896), including 18% (80/448) for cancers and 19% (83/448) for benign lesions. Among these changed recommendations, the fraction having a beneficial effect (malignant: step up; benign: step down) was 68% (111/163), and the fraction having a detrimental effect (malignant: step down; benign: step up) was 32% (52/163) because of CAD (test for proportion, $P < .001$). The fractions having a beneficial effect from CAD were 78% (62/80) and 59 % (49/83) for cancers and benign lesions, respectively.

Among the 62 observations for cancers with a beneficial effect, 31 (50%) were changed from follow-up to a biopsy recommendation by 11 radiologists. Among the 49 observations for benign lesions with a beneficial effect, 17 (35%) were changed from biopsy recommendation to follow-up by 9 radiologists. Figure 2a shows a cancer in which the CAD helped four radiologists to improve their



a.

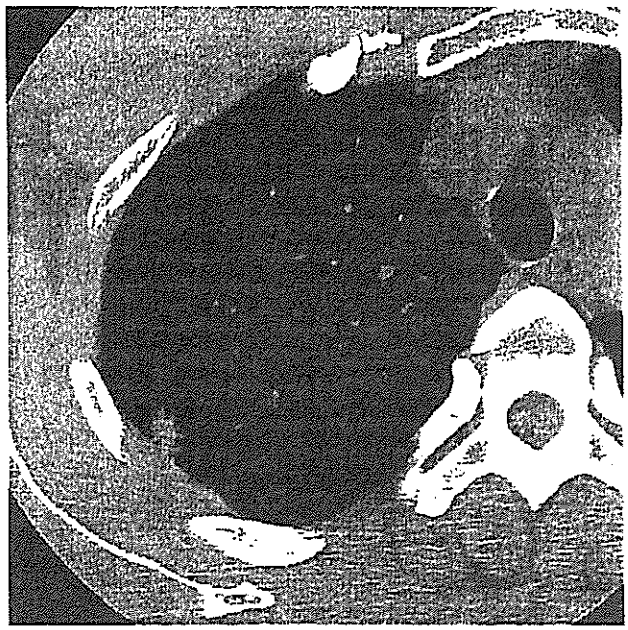


b.

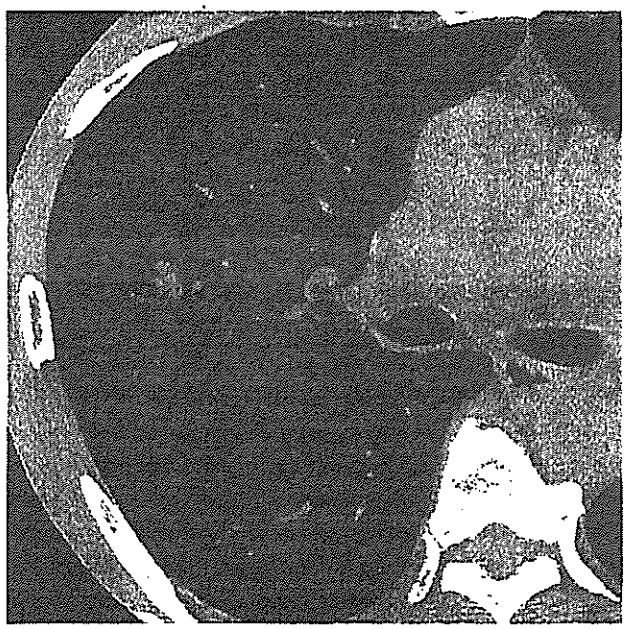
Figure 1. Graphs show the correlation between computer output and change in recommendations for 448 observations (28 cancers by 16 radiologists) **(a)** and 448 observations (28 benign lesions by 16 radiologists) **(b)**. The four recommendation steps are (1) follow-up in 12 months, (2) follow-up in 6 months, (3) follow-up in 3 months, and (4) biopsy. The numbers on the Y axis show the differences in recommendation indices between the without computer-aided diagnosis (CAD) and with CAD conditions: no change (0), step up (1, 2, and 3), and step down (–1, –2, and –3). The number of recommendations changed by radiologists by use of CAD was 163 (18%) for all 896 observations. Among these changed recommendations, the fraction toward a beneficial effect (malignant: step up; benign: step down) because of CAD was 68% (111/163) ($P < .001$).

recommendation from follow-up to biopsy. Figure 2b shows a benign lesion in which the CAD helped four radiologists to improve their recommendation from biopsy to follow-up.

Table 1 lists the number of lesions grouped based on radiologists' confidence ratings at three levels and recommendations in four steps for 896 observations (448 malignant and 448 benign) without and with CAD. There was no statistical significance in the biopsy recommendations between radiologists without and with CAD for cancers (38% = 170/448 versus 42% = 189/448; $P = .22$), although the number was increased from 170 to 189. For benign lesions, there was also no statistical significance in biopsy recommendations (13% = 57/448 versus 11% = 50/448; $P = .54$). The results indicate that the effect was not significant in the total proportion of radiologists' recommendations regarding biopsy by use of CAD.



a.



b.

Figure 2. Thin-section computed tomography images in two patients. **(a)** Computer-aided diagnosis (CAD) (likelihood of malignancy: 71%) helped four radiologists to alter their recommendation from follow-up to biopsy for a 47-year-old man with a squamous cell carcinoma. **(b)** CAD (likelihood of malignancy: 5%) helped four radiologists to alter their recommendation from biopsy to follow-up for a 63-year-old man with a benign lesion (no change for more than 3 years).

Table 2 shows the distribution of size and pattern of lesions for which radiologists made biopsy recommendations without and with CAD. The difference was statistically significant between a beneficial effect (benign: removed from biopsy; malignant: added to biopsy) and a detrimental effect (benign: added to biopsy; malignant: removed from biopsy) because of CAD (69% = 48/70 versus 31% = 22/70; test for proportion, $P = .002$). The difference was statistically significant between a beneficial effect and a detrimental effect with CAD for cancers (72% = 31/43 versus 28% = 12/43; $P = .003$), but the difference was not statistically significant between them with CAD for benign lesions (63% = 17/27 versus 37% = 10/27; $P = .18$). The results indicate that the changes regarding biopsy recommendations from CAD occurred less frequently for small lesions and lesions with pure GGO.

Table 3 shows the proportion of high confidence ratings (67%–99%) and recommendations for all lesions (malignant and benign) in three subgroups. The difference was statistically significant in the fraction of biopsy recommendations without CAD between lesions at 6–10 mm and lesions at 11–20 mm (32% = 10/31 versus 77% = 158/204; $P < .001$). The difference also was statistically significant for the fraction of biopsy recommendations with CAD between the 6- to 10-mm lesions (31% = 11/35) and the 11- 20-mm lesions (73% = 185/252) ($P < .001$). The difference was statistically significant in the fraction of biopsy recommendations without CAD within three patterns (pure GGOs: 27% = 12/44; mixed GGOs: 81% = 81/100; and solid lesions: 82% = 75/91; multiple-group test $P < .001$). Further, the difference was statistically significant for the fraction of biopsy recommendations without CAD between pure GGOs and mixed GGOs ($P < .001$) or solid lesions ($P < .001$). There was no statistically significant difference between the mixed GGOs and solid lesions without CAD ($P = .95$). The difference also was statistically significant for the fraction of biopsy recommendations with CAD within pure GGOs (26% = 16/62), mixed GGOs (78% = 92/118), and solid lesions (82% = 88/107) ($P < .001$), and between pure GGOs and mixed GGOs ($P < .001$) or solid lesions ($P < .001$). There was no statistically significant difference between the mixed GGOs and solid lesions with CAD ($P = .53$). The results indicate that radiologists also did not often recommend biopsy for the lesions between 6 and 10 mm and pure GGO lesions even when they indicated a high level of suspicion for cancer, regardless of CAD.

Table 1
Number of Lesions Grouped Based on Three Levels of Radiologists' Confidence and Four Different Recommendations for Lesions Without and With Computer-Aided Diagnosis (CAD)

	Confidence Levels Without CAD				Confidence Levels With CAD			
	1%–33%	34%–66%	67%–99%		1%–33%	34%–66%	67%–99%	
Recommendations	Malignant/Benign			Total	Malignant/Benign			Total
Biopsy	1/0	32/26	137/31	170/57	1/0	22/20	166/30	189/50
Other	79/269	141/113	58/9	278/391	63/287	118/98	78/13	259/398
Follow-up in 12 months	15/98	5/7	0/0	20/105	7/94	3/5	0/0	10/99
Follow-up in 6 months	39/92	48/27	7/1	94/120	29/110	41/28	9/1	79/139
Follow-up in 3 months	25/79	88/79	51/8	164/166	27/83	74/65	69/12	170/160
Total	80/269	173/139	195/40	448/448	64/287	140/118	244/43	448/448

Data are total 896 observations (56 lesions by 16 radiologists), including 448 observations with cancers (28 lesions by 16 radiologists) and 488 observations with benign nodules (28 lesions by 16 radiologists). There was no statistical significance in the biopsy recommendations between radiologists without and with CAD for both cancers (38% = 170/448 versus 42% = 189/448; $P = .22$) and benign lesions (13% = 57/448 versus 11% = 50/448; $P = .54$).

Table 2
Distribution of Lesion Sizes and Patterns for which Radiologists Made Biopsy Recommendations for Lesions Without and With CAD

	Biopsy Recommendations Without CAD	Biopsy Recommendations With CAD	Number ($n = 70$) With Beneficial (Detrimental) Effect From CAD
	Malignant/Benign	Malignant/Benign	Malignant ($n = 43$)/Benign ($n = 27$)
Total	170/57	189/50	31 (12)/17 (10)
Size			
6- to 10-mm lesion	12/5	13/1	3 (2)/4 (0)
11- to 20-mm lesion	158/52	176/49	28 (10)/13 (10)
Pattern			
Pure GGO	14/3	15/4	4 (3)/0 (1)
Mixed GGO	82/20	89/11	13 (6)/10 (1)
Solid	74/34	85/35	14 (3)/7 (8)

CAD, computer-aided diagnosis; GGO, ground glass opacity.

The difference was statistically significant between beneficial effect (malignant: 31 added to biopsy; benign: 17 removed from biopsy) and detrimental effect (malignant: 12 removed from biopsy; benign: 10 added to biopsy) with CAD (69% = 31 + 17/70 versus 31% = 12+10/70; $P < .002$). The difference was statistically significant between a beneficial effect and a detrimental effect with CAD for cancers (72% = 31/43 versus 28% = 12/43; $P = .003$), but the difference was not statistically significant between them with CAD for benign lesions (63% = 17/27 versus 37% = 10/27; $P = .18$). Also the results indicate that the changes regarding biopsy recommendations due to CAD were less occurred for small lesions and lesions with pure GGO.

DISCUSSION

Radiologists' recommendations with use of CAD have been investigated in several observer studies (3,5,6). Some studies showed that there was a significant beneficial effect resulting from classification CAD by increasing biopsy recommendations for breast cancers (5,6) with reduction (6) or no significant change in biopsy recommendations (5) for benign masses. In these studies, no further details were given for the effect of CAD on radiologists' recommendations—for example, how CAD affected radiologists' recommendations concerning different lesion sizes or patterns and why radiologists changed their recommendations for some lesions, but not others.

Observer studies with pulmonary nodules indicated similar results for the improvement of radiologists' performance in detecting lesions and distinguishing benign from malignant lesions on chest radiographs (10–12) and on chest CT scans (8,13–16). In our recent CT studies, we also asked radiologists to indicate their recommendations after they detected suspicious lung lesions (16) or after they had classified small lesions as

Table 3
Proportion of High Confidence Ratings (67%–99%) and Recommendations for All Lesions (Malignant and Benign) in Three Subgroups

	Biopsy Recommendations Without CAD	Biopsy Recommendations With CAD
Size		
6- to 10-mm lesion	32% (10/31)	31% (11/35)
11- to 20-mm lesion	77% (158/204)	73% (185/252)
Pattern		
Pure GGO	27% (12/44)	26% (16/62)
Mixed GGO	81% (81/100)	78% (92/118)
Solid lesion	82% (75/91)	82% (88/107)

CAD, computer-aided diagnosis; GGO, ground glass opacity.
The difference was statistically significant regarding the fraction of biopsy recommendations between the 6- to 10-mm lesions and the 11- to 20-mm lesions without (32% versus 77%; $P < .001$) and with (31% versus 73%; $P < .001$) CAD, and between pure GGOs and mixed GGOs or solid lesions without (27% versus 81% or 82%; $P < .001$) and with (26% versus 78% or 82%; $P < .001$) CAD. The results indicate that radiologists did not often recommend biopsy for small lesions and lesions with pure GGO, even when their level of suspicion for cancer was high, regardless of CAD.

malignant or benign (8). The results indicated that our detection CAD scheme significantly improved radiologists' recommendations for small-cell lung cancers without any significant detrimental effect for false positives on thick-section CT (16). Our classification CAD scheme also significantly improved radiologists' recommendations for early lung cancers, without any significant detrimental effect for small benign lesions on thin-section CT (8). Our purpose in this study was to further evaluate how classification CAD can assist radiologists in improving their recommendations for two sizes (6–10 mm and 11–20 mm) and three patterns (pure GGO, mixed GGO, and solid lesion) of early lung cancers compared with benign lesions.

The findings in the previous work indicated that the improvements in radiologists' confidence ratings resulting from CAD were relatively uniform; the average A_z value was improved from 0.785 to 0.853 for all lesions, including from 0.812 to 0.892 for nodules with pure GGO; from 0.819 to 0.863 for nodules with mixed GGO; and from 0.784 to 0.844 for solid nodules (8). However, the results of the current study indicated that the improvement of radiologists' biopsy recommendations resulting from CAD occurred mostly for larger lesions (11–20 mm) and lesions with mixed GGO or solid opacity. In other words, the current study indicated that the changes in biopsy recommendations were often dependent on lesion sizes or patterns. Radiologists' recommendations regarding biopsy were not often changed for smaller lesions or lesions with pure GGO resulting from CAD although the performance of CAD was also good for classification of these lesions.

We did not give any pretest training regarding interpretative guidelines for recommendations to radiologists in this observer study. However, several CT studies regarding the frequency of malignancy in different sizes and patterns, and regarding the growth rates of the cancers in different patterns, have been published previously (17–26). In the past decade, CT has been applied widely for early lung cancer screening (17–25), and radiologists have learned how lesion size and pattern relate to the probability of malignancy, and how histology affects tumor morphology. For example, the frequency of malignancy was very low for lesion sizes smaller than 10 mm in diameter in a screening program (23), and also in a clinical study (26). GGO lesions are more likely to be malignant than are solid ones in CT screening programs for lung cancer (9,24). In Hasegawa's series, almost all of the GGO lesions were slowly growing lung adenocarcinomas and the mean volume-doubling time of tumors with pure GGO was very long (more than 800 days) (25). Recently, guidelines for management of small pulmonary nodules detected on CT scans have been published (27). In the statement from the Fleischner Society (27), biopsy recommendations are only suggested as an option for lesions larger than 8 mm, whereas long follow-up intervals are appropriate for pure GGOs or very small opacities. These data help explain why radiologists in our study did not often recommend biopsy, even when their level of confidence for cancer was high, regardless of CAD, for the smaller and nonsolid lesions. We believe that radiologists' propensity to recommend biopsy may depend on their perception as to whether the lesion, if cancerous, is likely to grow quickly.

The limitations in this study include the small numbers of malignant and benign lesions. However, the dataset was obtained from a lung cancer CT screening program, which included three different CT patterns for both malignant and benign lesions. We believe that it is more difficult for to distinguish small benign lesions from early lung cancers in similar patterns, especially when distinguishing those lesions with GGO. Therefore, we used a special case subset, which included the most difficult

cases in differentiating benign from malignant lesions, in this observer study. There was no case bias for malignant lesions because the 28 lung cancers used in this observer study were selected randomly among our database, and only the 28 benign lesions were selected by matching their patterns and sizes to the cancers. Importantly, with our CAD scheme, the radiologists' performance was improved regarding biopsy recommendations for solid lesions or lesions with mixed GGO at relatively larger sizes. CAD has the potential to be useful for improving management of patients with small lung lesions on CT in clinical practice or in lung cancer screening programs.

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16. 低線量 CT による肺癌検診の資格認定の必要性

長　尾　啓　一

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