Table 4 Sensitivity of screening by the incidence method; (a) low-dose CT group and (b) chest X-ray group

	Person-years	Expected incidence	Screen-detected cases	Interval cases	Sensitivity (%) (95% CI)
(a) Low-dose CT group					
Sex					
Men	9173	21.8	29	3	86.2 (71.8–100)
Women	5512	2.5	11	2	20.0 (0–69.6)
Smoking status					
Nonsmokers	4878	1.7	13	0	100
Ex-smokers	2388	4.2	6	1	76.2 (35.5–100)
Current smokers	7419	18.6	21	4	78.5 (59.8–97.2)
Total	14 685	24.4	40	5	79.5 (63.5–95.5)
(b) Chest X-ray group					
Sex					
Men	17 962	42.1	15	8	81.0 (69.1–92.8)
Women	41 763	17.2	14	0	100
Smoking status					
Nonsmokers	42 976	17.4	13	0	100
Ex-smokers	8452	19.2	4	3	84.3 (68.1–100)
Current smokers	8297	22.8	12	5	78.1 (61.1–95.1)
Total	59 725	59.3	29	8	86.5 (77.8–95.2)

CI = confidence interval; CT = computed tomography.

screenings was significantly higher than that of the initial screenings. The high specificity associated with repeated screenings is due to the fact that the review of previous images facilitates ruling out benign nodules. Sensitivity of low-dose CT and chest X-ray for the repeated screenings was lower than that of the initial screenings; however, the difference was not statistically significant. Sensitivity for the initial screenings was affected by length bias and overestimation because lung cancers with long preclinical detectable phases were more prevalent. Regarding histological type, adenocarcinoma sensitivity estimated by the detection method was significantly higher than that for nonadenocarcinoma for both low-dose CT and chest X-ray. In the previous study, sensitivity of chest X-ray was 86.4% for adenocarcinoma and 44.2% for nonadenocarcinoma (Sobue *et al*, 1991c). Both low-dose CT screening and chest X-ray screening have a high sensitivity for the detection of adenocarcinoma. In contrast, sensitivity estimated by the detection method for nonadenocarcinoma remained low. As for smoking status, both low-dose CT and chest X-ray had superior performance for nonsmokers.

Although the detection method is simple and widely used, it is affected by overdiagnosis or length bias because cancers with long preclinical detectable phases are included in the denominator. In the 1980s, lung cancer was considered to be an aggressive and rapid-growing cancer; however, it has been reported that low-dose CT screening-detected lung cancer has a long doubling time and good prognosis (Sone *et al*, 2001; Nawa *et al*, 2002; Sobue *et al*, 2002a; Swensen *et al*, 2002; Henschke *et al*, 2006; Libby *et al*, 2006). The incidence method, which is not affected by overdiagnosis bias and length bias, is preferred for the correct evaluation of low-dose CT screening. Screening for breast cancers or colorectal cancers, with long doubling times, has been evaluated using the incidence method whereas lung cancer screening has been evaluated using the detection method only (Fletcher *et al*, 1993; Zappa *et al*, 2001).

In this study, we calculated expected lung cancer incidence to be 24.4 persons for the low-dose CT group and 59.3 persons for the chest X-ray group according to age-specific lung cancer incidence rate in the OCR, smoking status in Osaka prefecture and the relative risk of lung cancer incidence associated with smoking according to a large-scale cohort study in Japan. Unexpectedly, the sensitivity of low-dose CT screening estimated by the incidence method (79.5%) was lower than that of chest X-ray screening (86.5%); however, the difference was not statistically significant. There are several possible explanations for this contradiction. First, the mean follow-up term of the low-dose CT group (3.1 person-years) was shorter than that of the chest X-ray group (4.5 person-years). Furthermore, the mean pack index of current smokers among the low-dose CT group (42 for men and 23 for women) was somewhat higher than that of the chest X-ray group (38 for men and 16 for women). Therefore, expected lung cancer incidence for the low-dose CT group might be underestimated. Second, four screen-detected cases among the chest X-ray group were checked with lesions other than cancer. These lung cancer cases were incidentally detected by the subsequent chest CT as a further examination on positive tests; all of them were adenocarcinoma. When these cases were regarded as interval cases, sensitivity (95% confidence interval) of chest X-ray screening by the incidence method resulted in 79.7% (69.5–90.0%). Considering these points, sensitivity of low-dose CT screening according to the incidence method with 3–5 person-years of follow-up period would be almost equal to that of chest X-ray screening. These findings suggest that the efficacy of low-dose CT screening might be limited to rapid-growing lung cancer with a short preclinical detectable phase ($<=1$ year). Since low-dose CT screening-detected lung cancer is slow growing, further research with a longer follow-up period is required.

A total of 40 lung cancer cases were detected by low-dose CT screening, suggesting the possibility of overdiagnosis by low-dose CT screening. In particular, low-dose CT screening detected 13 lung cancer cases in nonsmokers whereas expected incidence in nonsmokers was only 1.7 persons. All of these cases were peripheral adenocarcinoma. In contrast, expected lung cancer incidence for the chest X-ray group was higher than the number of screen-detected cases. This fact might suggest that there is little possibility of overdiagnosis by chest X-ray screening.

Of the five interval cancer cases in the low-dose CT group, four cases were squamous cell carcinoma or small cell carcinoma, which are strongly associated with smoking (Sobue *et al*, 1991d; Shimizu *et al*, 1994; Stellman *et al*, 2001). Three cases had remarkable emphysaema. These interval cancer cases associated with smoking indicate the limitation of low-dose CT screening for

nonadenocarcinoma among smokers. In other words, the high sensitivity of low-dose CT screening identified using the detection method is due to the detection of adenocarcinoma with a long preclinical detectable phase.

This study has some limitations. First, many nodules were detected by low-dose CT screening, but subsequent pathological examinations were not performed. In this study, small pure ground-glass opacity nodules (<10 mm) were carefully observed, and no invasive treatment was performed. In these cases, lung cancer was highly suspected, but a lung cancer diagnosis was not made and the cases were not registered in the OCR. Given the presence of such cases, the sensitivity according to the detection method might be underestimated. Second, to compare usual screening with low-dose CT screening, the preclinical detectable phase was assumed to be 1 year. We need to assess a longer preclinical detectable phase, because most of the low-dose CT screening-detected lung cancer cases were slow growing. Third, the sample size was relatively small for proper evaluation, particularly for stratified analyses.

In summary, the present findings suggest that lung cancer screening using low-dose CT has a higher sensitivity and a lower specificity than usual lung cancer screening by chest X-ray, when using the detection method analysis. However, sensitivity estimated by the incidence method was not as high as that estimated by detection method. As all interval cancer cases were associated with smoking, low-dose CT screening showed limited efficacy for nonadenocarcinoma in smokers. Furthermore, these findings demonstrate the potential for overdiagnosis in low-dose CT screening-detected cases.

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Lung cancer screening—Comparison of computed tomography and X-ray

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Summary Recent studies on lung cancer screening with CT disclosed a discrepancy between its efficiency in detecting early lung cancer and a lack of proof for decreasing mortality from lung cancer. The present study, in a city in Japan where an X-ray screening program is provided, bi-annual CT screening was performed for X-ray screening negative subjects for 4 years. Ten patients with lung cancer were detected among 22,720 person-year subjects (0.044%) through the X-ray screening. Among the X-ray screening-negative subjects, 3305 subjects participated in a CT screening program resulting in the detection of 15 patients with lung cancer (0.454%). All 15 cases detected by CT screening and 5 of the 10 cases detected by X-ray screening were at stage IA. In respect of gender, histological type and CT findings, patients detected by CT screening had a better prognostic profile than those detected by X-ray screening. Survival was significantly better in the former than the latter, both in its entirety comparison and in a comparison limited to patients who underwent surgery. In conclusion, CT screening might have the potential to detect lung cancer with good prognostic factors not limited to early detection. Sufficiently long follow-up time, therefore, would be required to evaluate the efficacy for decreasing lung cancer mortality with CT screening.

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1. Introduction

Lung cancer is the leading cause of cancer death in many countries worldwide. Hope of decreasing death from lung cancer by early detection has encouraged studies for lung cancer screening by chest X-ray [1–4], sputum cytology and low-dose spiral computed tomography (CT) [5–13].

Recently, a large scale study on lung cancer screening by CT (International Early Lung Cancer Action Program, or I-ELCAP) resulted in a diagnosis of lung cancer in 484 participants out of 31,567 asymptomatic persons at risk for lung cancer, a high ratio of clinical stage I of 85% in the diagnosed patients, and a high estimated 10-year survival rate of 88% in the subgroup with clinical stage I lung cancer, confirming the previous reports on CT screening [10]. On the other hand, another international study failed to show a decline in advanced lung cancer diagnoses and lung cancer deaths by CT screening when compared with estimated numbers by means of 2 prediction models, although it again disclosed significant efficacy in the early detection of lung cancer [14], revealing a discrepancy between the studies. Clarifying the characteristics of lung cancer detected by CT screening may help to explain this discrepancy. The present study, performed in a single region, compared the results of lung cancer screenings by low-dose CT with those by conventional chest X-ray in terms of efficacy and the characteristics of the detected lung cancers.

2. Materials and methods

2.1. Study region and subject recruitment

The study was conducted in an anonymous city located in a suburb in Chiba prefecture next to Tokyo, Japan. The municipal office has, for decades, provided its residents older than 40 years with an annual health-screening program including chest X-ray. All subjects participating in this program, on the day of the chest X-ray screening, were informed of the free-of-charge and research-based low-dose CT screening program to take place at a later date, together with its potential benefits and risks. Those who gave their written informed consent for the study became candidates for enrolling in the CT screening for lung cancer. Subjects who had abnormalities detected on the basis of the X-ray screening, and were judged to require further examinations, were excluded from enrollment in the CT screening program. New subjects were recruited every year for each screening. With encouragement, repeat of the screening at the next opportunity depended on the individual's will.

2.2. Lung cancer screening by chest X-ray and CT

For screening with X-ray, images in 10×10 cm miniature radiograms were obtained with mobile X-ray equipment (Model MXO-15B, Toshiba Medical Systems Co., Otawara, Japan) on X-ray film rolls (X-ray film HX, Konica Minolta Holdings, Inc., Tokyo, Japan) with an X-ray mirror-camera (CM5-100, Canon Inc., Tokyo, Japan). The technical parameters consisted of tube voltage of 130 kV with adjustment of mAs by photo-timer, and a distance of 120 cm from the tube to film with a 2.0-mm aluminum filter. The film rolls were reviewed on dedicated illuminant miniature X-ray film viewers equipped with magnifying glasses. For screening with CT, images were obtained by mobile low-dose spiral CT equipment (W950SR, Hitachi Medical Co, Tokyo, tube voltage of 120 kV, electric current of 50 mA, rotation of $0.5\,s^{-1}$, collimation of 10 mm, interval of 10 mm). The images were reviewed on CRT with personal computer-based viewing and reporting system. Each image of X-ray and CT was reviewed by 2 independent expert pulmonologists, and any pulmonary or endobronchial nodule suggesting a lesion requiring further examinations was compared with a previous study when available. Then, the final judgment was given by several reviewers' consensual decision and the results were classified into 4 categories; no nodule (category I), nodules requiring no further examinations (category II), nodules suggesting non-malignant lesion requiring further examinations (including lesions suggesting active tuberculosis, category III), and nodules suggesting malignant lesions (category IV). There was no communication between X-ray and CT reviews. Further examinations consisted of conventional-dose CT with thin-section scanning, ranging from 0.5 to 2 mm thickness according to the requirement, in all patients with categories III and IV, follow-up studies by CT, and invasive diagnostic procedures including bronchoscopy, CT-guided biopsy and video-assisted thoracotomy when required.

The X-ray screening was repeated every year. Because of research resource limitation, the city was geographically divided into 2 areas, and the CT screening was performed alternatively in only one area each year, resulting in screening in the same area every 2 years. Inter-screening tracking of the subjects without categories III and IV was not allowed because of local regulations. Both screenings were performed from 2001 to 2004 in each fiscal year, with follow-up periods until September 2007. The entire study was approved by the Ethics Committee of the Chiba Foundation for Health Promotion & Disease Prevention.

2.3. Image analysis of detected lung cancer

Thin-section images of detected nodules definitively diagnosed as primary lung cancer were retrospectively reviewed and classified into 3 categories; pure ground glass attenuation (GGA), part solid (GGA with a central solid part) and solid nodule [15,16].

2.4. Statistics

Comparisons of frequency were performed by Student's t-test, and survival curves were drawn by Kaplan–Meier's method followed by comparison with log rank test. Differences with p values of less than 0.05 (two tailed) were judged as statistically significant.

3. Results

The total numbers of person-years for X-ray and CT screening in the 4-year period were 22,720 and 3305, with actual subject numbers of 8246 and 2550, respectively. Characteristics of the subjects are summarized in Table 1. In this

Table 1 Characteristics of subjects

Year	Total no. of subjects	Age (years)[a]	Sex		No. of baseline study	No. of repeat study
			No. of male (median age; range)	No. of female (median age, range)		
X-ray screening						
2001	5,309	59 (40–93)	1776 (63; 40–85)	3,533 (57; 40–93)	101	5,208
2002	5,417	58 (40–89)	1828 (62; 40–86)	3,589 (56; 40–89)	927	4,490
2003	5,782	59 (40–92)	2018 (63; 40–88)	3,764 (57; 40–92)	848	4,934
2004	6,212	60 (40–94)	2167 (63; 40–91)	4,045 (58; 40–94)	794	5,418
Total	22,720*	59 (40–94)	7789 (63; 40–91)	14,931 (57; 40–94)	2670	20,050*
CT screening						
2001 (area A)	729	65 (50–87)	326 (65; 50–85)	403 (66; 50–87)	729	NA
2002 (area B)	762	65 (50–84)	314 (66; 50–84)	448 (64; 50–81)	762	NA
2003 (area A)	838	65 (50–85)	361 (65; 50–83)	477 (64; 50–85)	519	319
2004 (area B)	976	65 (50–83)	419 (65; 50–83)	557 (64; 50–80)	540	436
Total	3,305*	65 (50–87)	1420 (65; 50–85)	1,885 (65; 50–87)	2550	755

[a] Median (range).
* Numbers in terms of person-years.

table, the actual number for CT screening is equal to the total number of subjects who participated in the baseline study because the screening was started at 2001. However, in the X-ray screening, the number of subjects participated in the repeat study at 2001 ($n = 5208$) plus total number of subjects participated in the baseline study ($n = 2670$) dose not result in the actual total number ($n = 8246$) in 4 years, because the screening had been started before 2001; there were some subjects who had participated in the screening before 2001 and did not at 2001. In addition, the subject number of repeat study is greatly exceeds the number of baseline study in every year, because many subjects had already participated in the screening before 2001. Smoking status of the subjects is summarized in Fig. 1 according to gender and screening method. The subjects of CT screening consisted of a significantly higher proportion of smokers than those of X-ray screening ($p < 0.001$ for males, and $p = 0.0014$ for females, χ^2 test). Total accrual numbers of further examinations (categories III and IV) were 313 (78 category III and 235 category IV) of 22,720 (1.4%) in X-ray screening, and 337 (67 category III and 270 category IV) of 3305 (10.2%) in CT screening.

All lung cancers were found exclusively from category IV in both screenings. Lung cancers were found in 10 patients (0.044% of the 22,720 screened) through the X-ray screening, 4 patients by baseline (0.1498%, or 4 out of 2670) and 6 patients by repeat screening (0.030%, 6 out of 20,050). Among them, 5 (50%) patients had stage IA lung cancer. With CT screening, 15 patients (0.454% of the 3305 screened) with primary lung cancer were found. They were exclusively found in baseline screening, and all 15 lung cancers were stage IA. Patient characteristics are summarized in Table 2. With X-ray screening, lung cancer was detected in 0.040% (6/14,931) of female participants, and in 0.051% (4/7789) of male participants, with a female-to-male ratio of the detection rate of 0.78. In contrast, with CT screening, it was detected in 0.58% (11/1885) of female, and in 0.28% (4/1420) of male participants, with a female-to-male ratio of 2.07. The proportion of adenocarcinoma was 86.7% (13/15) in patients detected through CT screening, significantly higher than that (50%, or 5/10) in patients detected through X-ray screening ($p = 0.0455$, χ^2 test). The constitution of the image type of lesions, that is, pure GGA, part solid and solid types, was significantly different between these 2 groups ($p = 0.0001$, χ^2 test), and those detected by CT screening were more likely to be pure GGA or part solid than those detected by X-ray screening. Standard lobectomy with hilar and mediastinal lymph node dissection was performed in 6 of the 10 lung cancer patients detected by X-ray and in 14 of the 15 patients detected by CT screening (Table 2). Retrospective re-review of X-rays of patients with CT screening-detected lung cancer disclosed that the corresponding lesion was visible on X-ray in only one case, #CT-12.

Survival curves of the patients with detected lung cancer are shown in Fig. 2. Survival of the patients detected by CT screening was better than that of the patients detected by X-ray screening with statistical significance (Fig. 2A). Survival of the patients undergoing surgery was also compared between the patient groups detected by CT and X-ray screenings, again disclosing better survival in the CT screened patients than in the X-ray-detected patients with

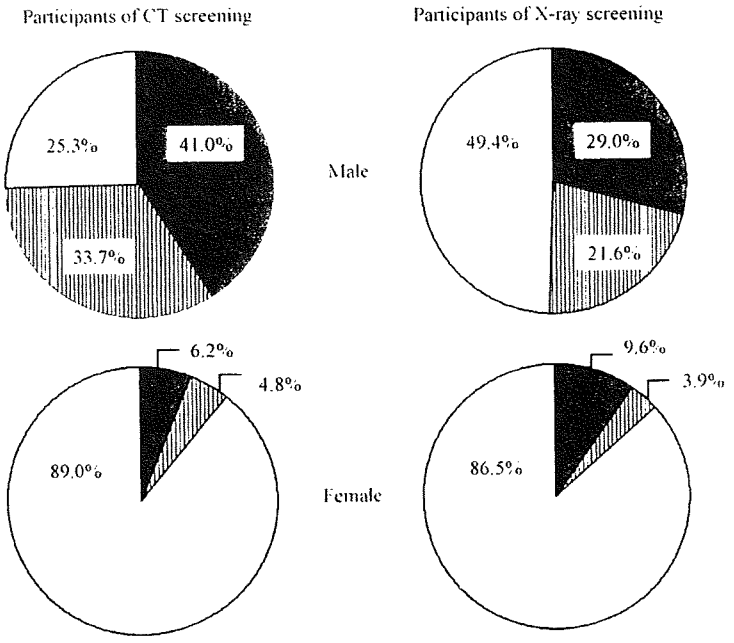

Fig. 1 Smoking status of the participants in the 2 screening programs. Closed, shaded and open areas represent current, ex- and never smokers, respectively. Smoking rates of the participants in the X-ray screening were similar to the general statistics in Japan, in both male and female populations, whereas those of the participants, especially in males, in the CT screening were significantly higher than in participants of the X-ray screening ($p < 0.001$ for males, and $p = 0.0014$ for females, χ^2 test), very possibly because of smokers' motivation to participate in CT screening.

Table 2 Characteristics of detected lung cancer

Case no.	Age	Sex	Size (mm)	Histology	Stage	Image type	Treatment	Visible on X-ray
With X-ray screening								
X-1	75	F	30[a]	Ad	p-IA	Solid	S[b]	NA
X-2	75	M	28	Sm	p-IB[c]	Solid	S and C	NA
X-3	70	F	20	Ad	p-IA	Solid	S	NA
X-4	77	M	50	Sq	c-IIIA	Solid	R	NA
X-5	74	M	20	Sq	c-IIIA	Solid	R	NA
X-6	78	F	8	Sm	c-IIIA	Solid	C and R	NA
X-7	51	F	25	Ad	p-IA	Solid	S	NA
X-8	47	M	27	Ad	c-IIIA	Solid	C and R	NA
X-9	69	F	10	Carcinoid	p-IA	Solid	S	NA
X-10	62	F	27	Ad	p-IA	Solid	S	NA
With CT screening								
CT-1	64	M	10	Ad	p-IA	Pure GGA	S	No
CT-2	72	F	11	Ad	p-IA	Pure GGA	S	No
CT-3	64	M	20	Ad	p-IA	Pure GGA	S	No
CT-4	63	F	15	Ad	p-IA	Part solid	S	No
CT-5	71	F	15	Ad	p-IA	Part solid	S	No
CT-6	79	M	14	Sq	p-IA	Solid	S	No
CT-7	66	F	7	Ad	p-IA	Pure GGA	S	No
CT-8	60	F	8	Ad	p-IA	Part solid	S	No
CT-9	67	F	15	Ad	p-IA	Part solid	S	No
CT-10	58	F	9	Ad	p-IA	Pure GGA	S	No
CT-11	63	F	10	Ad	p-IA	Pure GGA	S	No
CT-12[d]	59	M	23	Non-small	c-IA	Solid	BSC	Yes
CT-13	70	F	10	Ad	p-IA	Part solid	S	No
CT-14	62	F	10	Ad	p-IA	Part solid	S	No
CT-15	61	F	30	Ad	p-IA	Pure GGA	S	No

[a] Maximum diameter.
[b] S, R, C and BSC represent surgery, radiotherapy, chemotherapy and best supportive care, respectively.
[c] Postoperative evaluation of the tumor size determined the stage of IB.
[d] This patient was diagnosed as having clinical stage IA non-small cell lung cancer not further specified together with concomitant advanced esophageal cancer by staging procedures.

statistical significance (Fig. 2B). Two patients, detected by X-ray screening were dead after surgery, both from lung cancer recurrence (case #X-2 and 10).

4. Discussion

The present lung cancer screenings recruited subjects not limited to a high-risk group. First, the X-ray screening program was provided for general residents in a certain city in Japan, and the next screening program with CT was offered to the participants of the X-ray program, while excluding subjects who were judged to require further examinations by the X-ray screening. Therefore, the present CT screening program was eventually a screening for roentgen-negative lung cancer. The present study was preliminary and had several shortcomings: (1) sample size was relatively small, (2) there were some deviations in characteristics of the subjects; the subjects of X-ray screening consisted of less smokers and younger population especially in female than the subjects of CT screening, (3) examination was repeated every 2 years in the CT screening program, and (4) no inter-screening follow-up for counting lung cancer occurrence and death was performed, resulting in a lack of estimation of the true frequency of lung cancer occurrence in the subjects during the study period. In particular, the primary issues being the small sample size and the deviations in subject characteristics ostensibly limit this study's ability to make definitive conclusion. This kind of study solely enables us to evaluate screening efficacy by comparing CT screening with X-ray screening in terms of the characteristics of the detected lung cancer.

CT screening detected lung cancer at a frequency of approximately 10 times that of X-ray screening, even though CT screening was provided for X-ray screening-negative subjects. In addition, all lung cancers detected by CT were at stage IA, whereas only 6 of 10 lung cancers detected by X-ray screening were at stage IA, consequently resulting in better survival in the former compared to the latter. Characteristics of the lung cancer detected through CT screening were significantly different from those through X-ray screening. First of all, all 15 lung cancers detected by CT were adenocarcinomas except for one with non-small cell lung cancer not further specified, whereas only 5 of 10 lung cancers detected by X-ray screening were adenocarcinomas, the latter ratio being similar to that of the general statistics in Japan. Secondly, the female-to-male ratio of the detection rate with CT screening (2.07) was substantially higher than that with

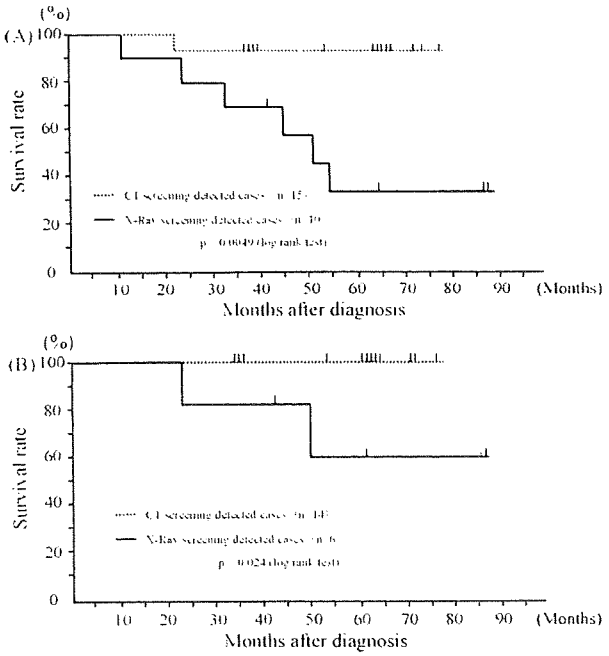

Fig. 2 Survival curves of patients with lung cancer according to screening method. Patients detected by CT screening ($n = 15$) survived significantly longer than patients detected by X-ray screening ($n = 10$, A). Comparison between the 2 groups limited to the subpopulations undergoing surgery showed a similar result (B). The curves were drawn by Kaplan–Meier's method, and compared with the log rank test.

X-ray screening (0.78). Considering that the female-to-male ratio of patients with lung cancer in the general statistics of Japan was 0.41 [17], the ratio with CT screening seemed extraordinarily high, and may actually be biased. As a matter of fact, the ratio with X-ray screening of 0.78 also seemed high, suggesting strong bias with screening. Thirdly, when assessed with thin-section CT, the image type of the lung cancer detected by CT screening contained a significantly larger portion of pure GGA or part solid type than that by X-ray screening. This is quite reasonable because nodules of GGA type are notoriously invisible on X-ray. The existence of GGA either as pure GGA or in part solid nodules in thin-section CT represents air-spaces in lung adenocarcinoma tissue, and very likely corresponds to either type A, B, or C of peripheral small adenocarcinoma [15,16,18–21] according to Noguchi's classification [22]. Such lung adenocarcinomas, in most cases, are characterized by a slow-growing nature and good prognosis with lung resection [15,16,18–22].

Effective cancer screening requires several conditions including the followings: (1) the screening is capable of detecting corresponding cancer at a high frequency, (2) prognosis of patients with screening-detected cancer is significantly better than that of patients found by symptoms, (3) less patients with advanced cancer and deaths from the cancer are shown by the screening, and (4) the screening is affordable in respect to human resource and cost. Many previous studies [5,11,13,23–27] and two recent studies [10,14] on lung cancer screening by CT provided evidence for the first 2 conditions. The present study also supports these previous study results. Bach et al., however, cast doubt on lower number of patients with advanced disease and lung cancer deaths by CT screening [14]. The discrepancy between the high frequency of early detection resulting in good prognosis of the detected patients and a lack of decrease in advanced disease and death may be partly explained by overdiagnosis through screening. That is to say, in spite of a definitive histological diagnosis, many early lung cancers detected through screening would not progress rapidly to the point of being clinically overt in the individual's lifetime. In fact, lung cancers detected via the present CT screening seemed to possess less malignant propensity, because the majority (13 out of 15 patients) were classified into either pure GGA or part solid type adenocarcinomas by thin-section CT findings, and because they were found predominantly in female non-smokers. In particular, detection and diagnosis in one patient (#CT-12) was apparently overdiagnosed because he died from concomitant advanced esophageal cancer while his lung cancer was at clinical stage IA. Nevertheless, the rest of the lung cancers detected by the present CT screening would have very possibly progressed to clinically overt and fatal cancer if left untreated, making it needless to refer in particular to the I-ELCAP study [10], in which 8 patients with clinical stage I cancer detected by CT screening did not receive treatment, with all of them dying within 5 years. In addition, any individual with pulmonary nodules judged to require further examinations through X-ray screening was excluded from enrollment to the CT screening. Most lung cancers detected by X-ray screening would have been detected by CT screening if no X-ray screening had been provided. Therefore, the present CT screening has the potential to reduce advanced lung cancer or death from lung cancer in the future, but not within a few years. Although Bach et al. failed to demonstrate a decrease in advanced disease and death from lung cancer [14], the reason for the negative result may be related to a relatively short median follow-up period of 3.9 years. Needless to say, large-scale randomized controlled studies that eliminate biases would have advantages for drawing definitive conclusions. Hence, results from randomized controlled studies such as the National Lung Screening Trial in the United States and the NELSON Trial in Europe are awaited [14,28,29]. It is important, however, to understand that a substantially long follow-up period, although difficult to be estimated from this study, would be required even in the case of well-sophisticated randomized controlled studies. Considerations on potential harm and cost would also be an important issue.

In conclusion, the present study confirmed the capability of CT screening in detecting early stage lung cancer at a high frequency, and suggested that CT screening-detected lung cancer might have less malignant propensity than X-ray screening-detected or symptom-detected lung cancer. In CT screening for lung cancer, a considerably extended follow-up period would be essential for evaluating its effectiveness in decreasing lung cancer mortality.

Conflict of interest

There exists no potential conflict of interest with regard to the manuscript in every author.

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原 著

岡山県における肺がん検診精検結果把握について

A study on accuracy improvement of lung cancer screening in Okayama Prefecture —Impact of a follow-up survey for diagnostic examination—

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Abstract

To reduce the mortality rate of lung cancer with a mass screening, improvement of accuracy is needed. Regarding an accuracy of lung cancer screening, it is important that how many of those who are recommended to have further examination actually have it. It is also important to know this percentage. In the procedure of lung cancer screening in Okayama Prefecture, we keep track of the information of further examination under combined effort of city governments or hospitals and gain good results. In our system, we send an original format regarding further examination with a stamped, self-addressed envelope. Collating with Okayama Cancer Registry in end of the year improved the accuracy of these rates. These efforts contribute us to recognize how many of those who are recommended to have further examination actually have it (66.1 % in 2003 to 97.8 % in 2005). This information helps doctors checking X-ray films and contribute the improvement of accuracy of lung cancer screening.

Keywords: lung cancer screening system, quality control, a follow-up survey

はじめに

わが国の2006年肺癌死亡数は63,255人と上昇を続けており[1]、がん対策のなかでも重要な問題になっている。そのため早期発見のための肺がん検診の役割は大きくなっているが、肺癌死亡率減少に効果のある肺がん検診には高い精度が求められることはいうまでもない。岡山県においては1976年から肺がん検診が開始されており、30年以上の経験をもとに岡山方式といわれる検診システムが構築されてきた。1987(昭和62)年に老人保健法に肺がん検診が組み込まれ、全国的に統一された制度がスタートしたが、その当時から高い精度の検診のみが肺癌死亡率減少につながる成果が期待できるといわれていた[2]。

最近行われた厚生労働省の垣添班の報告書でも、検診のあらゆる段階での高い精度管理が要求されている[3]。今回、精度管理のなかでも困難に直面している精検結果把握について岡山での取り組みを報告する。

対象および方法

われわれが行っている肺がん検診のうち、地域住民を対象とした肺がん検診を対象とした。岡山県の27市町村のうち17市町村(63%)で当財団の肺がん住民検診が行われている。肺がん検診は車載型間接X線100mmミラーカメラを用いて背腹一方向撮影が行われ、読影は2名の医師において独立して行い、経年受診者については前回フィルムとの比較読影を行って要精検者を決定している。2003年から05年までの3

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年間に肺がん検診を受診した40歳以上の住民は、延べ452,517人で発見された肺癌は301人、発見率は10万人対66.5であった（**表1**）。

検診フィルムの読影結果は肺癌取扱規約[4]の判定基準に従い、AからEの5段階で結果を通知した。E判定は「肺癌を疑い」、D判定は「肺癌以外の疾患を疑って精検」であるが、実際には両判定者に精検通知や精検受診勧奨の差をつけていない。精検依頼書は岡山県指定の様式のものを使用したが、医療機関から直接精検情報を取得して、追跡調査を容易にするため、当財団独自の結果調査票（**図1**）と返信用封筒（**図2**）も同封した。各年度終了時に岡山県医師会情報センターで行っている岡山県がん登録から、要精検者の精検結果を入手し、市町村ごとに肺癌発見数などの集計結果を報告し、市町村への情報の還元も行った。しかし、がん登録から得られる情報には不備が多いこと、医療機関からの登録がかなり遅れることが問題で、それを補うために独自の結果調査票による情報収集を行い、発見肺癌の詳しいデータを得るように工夫した（**図3**）。

表1　肺癌発見率

	男性	女性	計
全受診者	147,247	373,437	520,684
40歳以上受診者	137,631	314,886	452,517
発見肺癌	200	102	302
発見肺癌（40歳以上）	200	101	301
肺癌発見率（10万対）	145.3	32.1	66.5

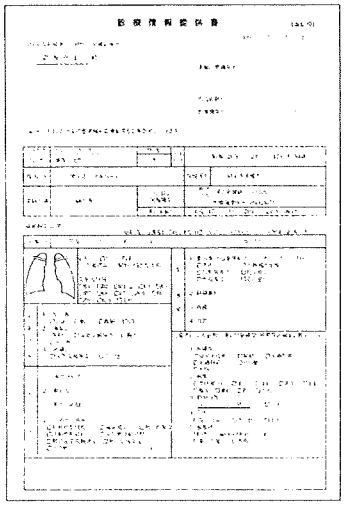

図1　財団独自の調査票

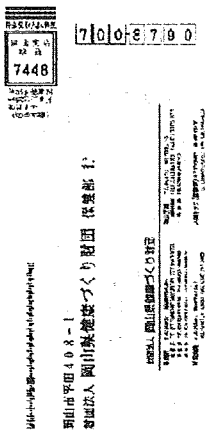

図2　返信用封筒

結　果

表2に2003年度からの肺がん検診の結果を示す。2003年度の受診者数は134,456名で、要精検は3,674名、要精検率2.73％であった。当財団で精検結果を把握できたのは2,427名（66.1％）であった。2004年度より医療機関への精検依頼に際し、当財団あての結果票と返信用封筒を同封したところ、精検把握率は78.1％に上昇した。2005年度、06年度と精検結果把握率は90％を大きく超えている。追跡調査を毎年行うことで、医療機関との連携や信頼関係が増し、結果票の回収率が増加して精検把握率の上昇が得られている。同期間に岡山県がん登録より提供されたデータでは、約60％の精検把握率で、しかも精検結果についても、組織や病期、治療法不明がかなりみられた（**図4**）。

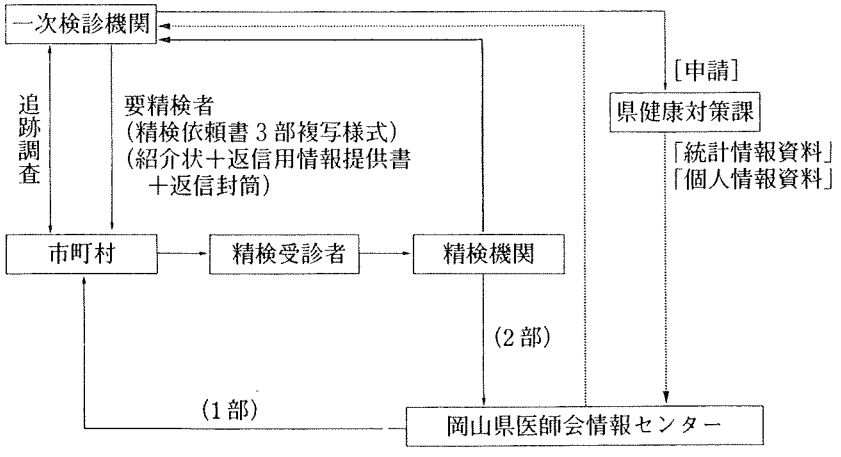

図3　精密検診結果収集財団方式

また2007年度を例に、胸部X線検診の受診から診断までの過程を示すと（**表3**）、間接X線二重読影後の要精検率は6.75％で、80％の経年受診者に比較読影を行うことで4.16％は精検不要となるので、

表2 各年度における精検結果把握率

	受診者数	要精検者数	要精検率	精検結果等状況把握数	把握率	把握時期
2003年度	134,456	3,674	2.73％	2,427	66.1％	2004.2.10
2004年度	129,593	2,922	2.25％	2,283	78.1％	2005.2.16
2005年度	109,263	2,829	2.59％	2,768	97.8％	2006.2.10
2006年度	97,089	2,822	2.91％	2,645	93.7％	2007.2.10

最終要精検率は2.59％と絞り込まれる。このうち肺癌疑いであるE判定は0.14％で、これらの症例は至急精検として、保健師を通じて個別に精検受診を勧奨しているが、胸部検診の特殊性として肺癌以外の要精検Dが2.45％とかなりの数にのぼる。制度上から考えると肺癌はE判定者からしかでないはずであり、がん登録から得られる情報も当然E判定者のみであるが、実際には間接X線読影段階で肺癌と肺癌以外を厳密に分けることは困難で、2007年度の集計でも、D判定から発見肺癌の半分以上の31例の肺癌が発見されており、これらの症例の情報は医療機関からの精検結果票に頼らざるをえない。

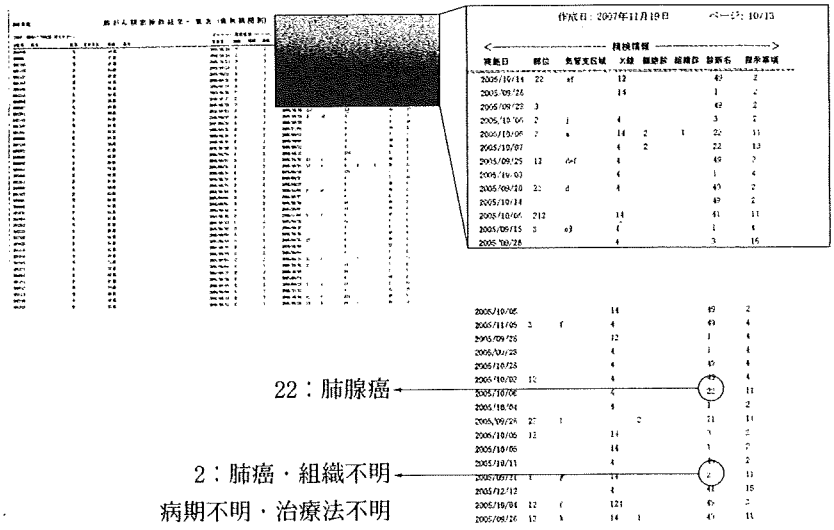

図4 がん登録から提供された情報

考 察

精検受診率は検診精度のなかでも大きな比重を占めるが、そのためには正確な精検結果の把握がぜひ必要である。精度の高い検診とは、早期癌を発見する読影力、肺癌が疑われた受診者にすみやかに結果を通知し、精密検査機関を紹介して確定診断・治療に至るシステム全体をいう。この過程でもっとも困難と考えられているのが精検結果の把握である。当財団が岡山県で肺がん検診を限られた市町村で始めた昭和50年代後半は、精密検査も当財団ですべて行い、全例精検結果を把握していた。治療を担当する医療機関も大学病院等に限られており、治療結果や予後の追跡も容易であった。しかし、1987（昭和62）年に老人保健法での肺がん検診が全市町村で実施されることになり、受診する地域や受診者数が急速に増加したため、精検担当医療機関も複数となり、追跡調査が必要になったが、市町村や医療機関と連携を図りながら比較的スムーズに行うことができた。ただ、肺がん検診は結核検診も兼ねており、結核予防法と老

表3 胸部X線検診の診断までの過程

2007年度		
受診総数		109,263 (100％)
間接X-P	二重読影にて	
	要精検 (d+e)	7,370 (6.75％)
	比較読影	
	精検不要	4,541 (4.16％)
	要精検 (D+E)	2,829 (2.59％)
	肺癌以外 D	2,678 (2.45％)
	肺癌 E	151 (0.14％)
原発性肺癌		58
転移性肺癌		11
肺癌疑い		56

人保健法による精密検査（DとE判定）が混在するため、一部の慣れない精検担当医療機関で肺癌疑い患者の診断確定までに3か月以上を要する場合もみられ、受診者からの批判も招いた。

その後、1998（平成10）年のがん検診の一般財源化により、肺がん検診の受診勧奨をほとんど行わない市町村も現れ、検診受診率の著しい低下と、肺癌発見率の低下が起こった。その後の市町村の大合併と結核予防法の廃止の影響を受け、肺がん検診受診者の減少傾向はさらに顕著になっている。肺がん検診の実施主体は各市町村であり、その担当者の熱意も検診精度に影響する。各県に設置されている生活習慣病検診管理指導協議会による市町村に対する働きかけも、担当者の意識改革に貢献するとの報告[5]もあり、積極的な同協議会の活用を検討したい。

精検結果の把握については、岡山県がん登録との照合で情報を得られるとの考え方もあったが、実際には得られる情報は60％と低率であった。実際の精検受診率が80％台であることを考えると乖離が大きく、その情報の信頼性に疑問がもたれたため、独自の結果票を同封することにした。当初は結果票のみを同封したが、医療機関に郵送料が発生することより回収率が低かったため、返信用の封筒も同封し、回収率上昇に寄与した。同様の現象は東京都予防医学協会の乳がん検診追跡の場合にもみられたと報告されている[6]。

当財団の精検完了率（把握率）は90％を超えていたが、2005（平成17）年の個人情報保護法の施行により、医療機関からの情報提供が著しく困難になり、がん登録からの情報提供にも制約が増えている。このままの状態が続けば、肺がん検診の信頼性を確保するのは難しい状態になると危惧しており、国による何らかの法的対策を期待したい。

精検結果の把握は検診システムの重要課題と考えられるが、それに加えて、検診フィルム読影医にとっては、発見時の画像にあわせて1年前のフィルム上の極めて早い時期の肺癌陰影を知る機会を得ることにもなる。肺癌の組織型、病期、治療方法までを詳細に把握することが、さらに肺癌の発見率を向上させるうえで重要であると認識される。

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要旨

日本がん検診・診断学会誌 16（3）：73-76、2009

肺がん検診により肺癌死亡率の減少を目指すためには、精度の高い検診を実施することが必要である。検診精度のなかで、もっとも重要なものは精検受診率の高さと、その結果の把握率の高さである。当財団で実施している肺がん検診システムにおいては、市町村・医療機関の協力を得て、要精検者の追跡調査を実施し、良好な結果を得ている。具体的には、当財団独自の精検依頼書を作成して、返信用の封筒を同封して医療機関から直接情報を得ている。年度末にOkayama Cancer Registryより提供される精検結果と照合することでさらに精度を向上させている。これらの努力により、2003年度は66.1％であった精検結果把握率が、2005年度には97.8％にまで向上した。こうして得られた情報は読影医師にも還元され、読影精度の向上にも役立っている。

キーワード：肺がん検診、追跡調査、精検結果把握

Prognostic Significance of Thin-Section CT Scan Findings in Small-Sized Lung Adenocarcinoma*

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Objectives: **The purpose of this study is to evaluate the prognostic importance of thin-section (TS) CT scan findings in small-sized lung adenocarcinomas.**

Patients and methods: **We reviewed TS-CT scan findings and pathologic specimens from 359 consecutive patients who underwent surgical resection for peripheral lung adenocarcinomas ≤ 20 mm in diameter during the period from July 1997 to May 2006. By using TS-CT scan images, tumors were defined as air-containing types if the maximum diameter of tumor opacity on mediastinal window images was less than or equal to half of that seen on lung window images, and as a solid-density type if the maximum diameter on the mediastinal window images was more than half of that on lung window images. We compared TS-CT scan findings to pathologic findings (*ie*, lymph node metastasis, pleural invasion, vessel invasion, and lymphatic invasion) and prognosis. The following prognostic factors were analyzed by χ^2 test and Cox proportional hazard model: age; gender; tumor size; pathologic stage; TS-CT scan findings; histologic subtypes defined by Noguchi et al (*ie*, Noguchi type); pleural involvement; lymphatic invasion; and vascular invasion.**

Results: **No pathologic invasive findings or recurrence were found in patients with air-containing-type tumors. Pathologic invasive findings and recurrence were found in 10 to 30% of patients with solid-density-type tumors. The air-containing type tumors seen on TS-CT scans and Noguchi type A or B tumors were demonstrated as prognostic factors for good outcome by χ^2 test ($p < 0.001$). Multivariate analyses revealed lymphatic permeation as a significant prognostic factor.**

Conclusion: **The TS-CT scan findings were important predictive factors for postsurgical outcome in patients with lung adenocarcinoma.** ***(CHEST 2008; 133:441–447)***

Key words: bronchioloalveolar cell carcinoma; ground-glass opacity; limited surgery; noninvasive cancer

Abbreviations: BAC = bronchioloalveolar cell carcinoma; GGO = ground-glass opacity; HU = Hounsfield units; TS = thin section

The number of patients with small-sized lung carcinoma has been increasing due to the routine clinical use of CT scanning and the increasing use of helical CT scan screening for lung cancer. Adenocarcinoma is the most common histologic type of lung cancer in those cases. The population of lung adenocarcinoma is heterogeneous, and many subtypes of adenocarcinoma have been advocated.[1,2] For example, Noguchi et al[1] classified small-sized lung adenocarcinoma into six subtypes based on tumor growth patterns. In this study, a type A or B tumor was localized bronchioloalveolar cell carcinoma (BAC), which showed no lymph node metastasis, rare vascular and pleural invasion, and excellent prognosis (5-year survival rate, 100%). A type C tumor was BAC with foci of active fibroblast proliferation, and showed pathologic invasive findings, and poor prognosis (5-year survival rate, 74.8%). A type D, E, or F tumor was adenocarcinoma without BAC and showed worst prognosis (5-year survival rate, 52.4%). Although these pathologic characteristics are useful as prognostic indicators, the results are defined only after surgery. If we have techniques by which we know the biological behavior of the tumor

and prognosis before treatment, they may be useful for planning therapy.

Many investigators reported that preoperative CT scan findings were related to the pathologic features and prognosis after resection of the tumor. The ratio of ground-glass opacity (GGO), defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking on the CT scan, was associated with the histologic type of the tumor and survival. One of the purposes of these studies was to determine noninvasive carcinoma, defined as a tumor without lymph node metastasis, pleural invasion, vascular invasion, and lymphatic invasion by using thin-section (TS) CT scan images. However, there are few articles accurately determining noninvasive carcinoma by TS-CT scan images. If we determine a diagnosis of noninvasive carcinoma using CT scan images, they are useful for deciding on the surgical procedure to be used, especially lesser resection. This study was carried out to determine whether TS-CT scan findings were good indicators of noninvasive carcinoma of the lung, and also to clarify whether TS-CT scan findings were related to the prognosis.

Materials and Methods

We reviewed TS-CT scan findings and pathologic specimens from 359 consecutive patients who underwent surgical resection for peripheral adenocarcinomas ≤ 20 mm in diameter during the period from July 1997 to May 2006. All patients underwent physical examination, chest roentgenography, CT scan of the chest and abdomen, bone scintigraphy, and MRI of the brain for the staging and evaluation of resectability before the operation. The patients with disease of clinical stage IIB or less underwent surgery. We also surgically treated the patients with clinical N2 disease without evidence of mediastinal lymph node metastasis proven by mediastinoscopy. This study was approved by our institutional review board after confirmation of informed consent by the patients for us to review their records and images. Chest CT scan images were obtained by a commercially available scanner (X-Vigor/Real or Aquilion M/16 CT scanner; Toshiba Medical Systems; Tokyo, Japan). Conventional CT scan images were obtained serially from the thoracic inlet to the lung bases at 120 kV peak spacing, 512 × 512 pixel resolution, and 1-s scanning time. TS images targeted to the tumor were obtained serially at 120 kVp and 200 mA, with 2-mm section thickness, pitch 1, section spacing of 1 to 2 mm, 512 × 512 pixel resolution, and 1-s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. These images were printed as photographs on each sheet of films using a mediastinal window level setting (level, 40 Hounsfield units [HU]; width, 400 HU) and a pulmonary window level setting (level, −600 HU; width, 1,600 HU).

While contrast medium (60 mL) was infused IV during imaging, lesion sites were translocated in a helical scan mode with a CT scan table speed of 2 mm/s; TS-CT scan images were obtained at one breath hold (120 kVp; 200 mA). The time interval between CT scan examination and subsequent surgery was ≤ 2 weeks in all patients. All CT scan images were reviewed by four thoracic oncologists who were not informed of the pathologic findings. They obtained the maximum dimension of the tumor using a pulmonary window level setting and the maximum dimension of the tumor using a mediastinal window level setting from the TS-CT scan images.

Tumors were defined as air-containing types if the ratio of the maximum dimension of the tumor using a mediastinal window level setting to the maximum dimension of the tumor using a pulmonary window level setting was ≤ 50%, and were defined as solid-density types if it was > 50%. Examples of CT scan images of the two groups are shown in Figures 1 and 2.

Each pattern based on TS-CT scan images was evaluated in terms of pathologic findings and survival outcome. We evaluated pathologic stage (TNM system), pleural involvement, vascular invasion, and lymphatic invasion. In addition, pathologic subtypes defined by Noguchi et al[1] (called hereafter *Noguchi type*) were evaluated.

The statistical significance of the difference between the incidence of relapse and TS-CT scan findings or Noguchi type was assessed by χ^2 tests. Relapse-free survival was calculated by the Kaplan-Meier method. Log-rank tests were used to compare the Kaplan-Meier curves. The Cox proportional hazards model was applied for multivariate analysis. Significance was defined as $p < 0.05$.

Results

Patient and tumor characteristics are listed in Table 1. There were 60 cases in which the largest diameter of the lesion was ≤ 10 mm, 130 cases in which it was 11 to 15 mm, and 169 cases in which it was 16 to 20 mm. There were 152 patients with air-containing-type tumors, and 207 patients with solid-density-type tumors. Table 2 shows the relationship between TS-CT scan findings and pathologic findings. No patients with air-containing-type tumors had lymph node metastasis, pleural involvement, vascular invasion, or lymphatic permeation. Among patients with solid-density-type tumors, 23 (11%) had lymph node metastasis, 45 (22%) had pleural involvement, 69 (33%) had vascular invasion, and 41 (20%) had lymphatic permeation. Table 3 shows the relationship between TS-CT scan findings and

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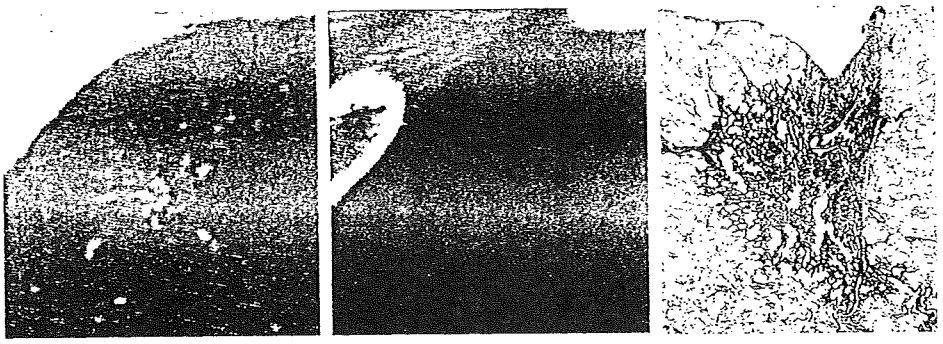

FIGURE 1. TS-CT scan findings of an air-containing-type tumor (diameter, 13 mm) on lung window setting images (*left*, *a*) and on mediastinal window setting images (*center*, *b*). The histologic specimen (*right*, *c*) shows BAC (hematoxylin-eosin, original × 6).

pathologic stage. All patients with air-containing-type tumors had pathologic stage IA disease. In contrast, 39 patients (19%) with solid-density-type tumors had pathologic stage IB or greater disease. Table 5 shows the relationship between TS-CT scan findings and Noguchi type tumors. Among 152 patients with air-containing-type tumors, 79 patients received lobectomy, while 73 underwent limited resections (*ie*, segmentectomy or wedge resection) because of their small size (median tumor diameter, 11 mm). Among 207 patients with solid-density-type tumors, 3 patients underwent pneumonectomy and 155 underwent lobectomy, while 49 underwent limited resections because of their being elderly or having pulmonary hypofunction.

Table 2 shows the relationship between TS-CT scan findings and cancer relapse after surgery. No postoperative cancer relapse was seen in patients with air-containing-type tumors; in contrast, relapse was found in 31 patients (15%) with solid-density-type tumors. The relapse-free survival of 207 patients for whom ≥ 3 years have passed since surgery is shown in Figure 3. Patients with air-containing-type tumors had a 100% 5-year relapse-free survival rate, which was significantly better than that for patients with solid-density-type tumors ($p < 0.001$).

We assessed prognostic factors in 207 patients for whom ≥ 3 years had passed since undergoing surgery. Table 5 shows the relationship between cancer relapse and TS-CT scan findings or Noguchi type. No cancer relapse was seen patients with air-containing-type tumors or patients with Noguchi type A or B tumors. The presence of both air-containing-type and Noguchi type A or B tumors were demonstrated as significant prognostic factors for good outcome by χ^2 tests ($p < 0.001$). The reason for using χ^2 tests but not Cox proportional hazards models to analyze the prognostic factors for TS-CT scan findings and Noguchi type tumors was due to the difficulty in conducting a statistical analysis at the time of no relapse event in the patient group with air-containing-type tumors or Noguchi type A or B tumors. Then, a multivariate analysis with a Cox pro-

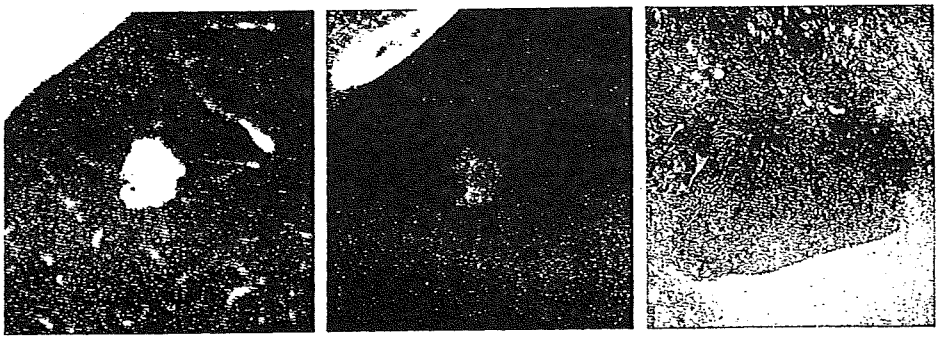

FIGURE 2. TS-CT scan findings for a solid-density-type tumor (diameter, 14 mm) on lung window setting images (*left*, *a*) and on mediastinal window setting images (*center*, *b*). The histologic specimen (*right*, *c*) shows poorly differentiated adenocarcinoma (hematoxylin-eosin, original × 6).

Table 1—*Patient and Tumor Characteristics**

Variables	Values
Patients, No.	359
Age, yr	29–86 (65)
Gender, No.	
Male	159
Female	200
Tumor size, mm	5–20 (15)
Noguchi type tumor, No.	
Type A	52
Type B	75
Type C	162
Type D	39
Type E	5
Type F	25
TS-CT scan findings, No.	
Air-containing-type tumor	152
Solid-density-type tumor	207

*Values are given as range (median) or No.

portional hazard model was performed in 116 patients without air-containing type tumors or Noguchi type A or B tumors. The results showed that lymphatic permeation was a significant prognostic factor (Table 6).

Discussion

In patients with small-sized lung adenocarcinomas, several authors[1,2] have shown that pathologic characteristics are correlated with prognosis. Noguchi et al[1] have used tumor growth patterns to classify small-sized adenocarcinomas into six subtypes (*ie*, types A to F). Small, localized BACs (*ie*, types A and B) have not yet metastasized to lymph nodes or invaded vessels or pleura, and are associated with an excellent prognosis (5-year survival rate, 100%). Localized BAC with central fibrosis formation (*ie*, type C) is thought to be advanced carcinoma, which progresses from type A or B and is associated with a poorer prognosis than before (5-year survival rate, 74.8%). The prognosis for patients with nonreplacement-type adenocarcinomas (*ie*, types D, E, or F) is worse than that for patients with replacement-type adenocarcinomas (*ie*, types A, B, and C) [5-year survival rate, 52.4%]. Suzuki et al[3] showed that the size of the central fibrosis was a prognostic factor among peripheral lung adenocarcinomas that were ≤ 3.0 cm in size. In this study, the patients with adenocarcinoma having central fibrosis ≤ 5 mm in the maximum dimension had a 5-year survival rate of 100%, whereas the other patients had a 5-year survival rate of 70%. Higashiyama et al[4] showed that the component area of BAC was correlated with postoperative survival in patients with small peripheral adenocarcinomas ≤ 2.0 cm in diameter. Patients with adenocarcinoma having a BAC component comprising < 50% of the tumor tissue showed a significantly poorer prognosis than those with ≥ 50%.

In TS-CT scan images, consolidation areas represent mostly the foci of fibrosis or tumors of a solid growth pattern, whereas GGO areas reflect areas of a growth pattern of tumor cells replacing alveolar lining cells such as BAC. Because the fibrotic foci increase with the progression of the tumor, and because these areas and advanced adenocarcinomas with a solid growth pattern demonstrate consolidation areas on CT scans, it is suggested that the percentage of the consolidation or GGO areas relative to the tumor is a prognostic indicator. Many investigators[5–22] have reported on the correlation among TS-CT scan findings, pathologic findings, and prognosis. These studies have shown that GGO ratios were very much associated with BAC ratios and had favorable prognostic factors. However, the methods used to calculate the percentage of GGO areas (*ie*, GGO ratio) differ in different articles. Besides, we have few articles that have accurately determined the presence of noninvasive carcinoma, which was defined as a tumor without lymph node

Table 2—*Relationship Between TS-CT Findings and Both Pathologic Findings and Recurrence*

Pathologic Findings	TS-CT Scan Findings: Air-Containing-Type Tumors (n = 152)	TS-CT Scan Findings: Solid-Density-Type Tumors (n = 207)
Lymph node metastasis	0	23
Pleural involvement	0	45
Lymphatic permeation	0	41
Vascular invasion	0	69
Recurrence	0	31

Table 3—*Relationship Between TS-CT Findings and Pathologic Stage*

TS-CT Scan Findings	Pathologic Stage: IA	IB	IIA	IIB	IIIA	IIIB
Air-containing-type tumor	152	0	0	0	0	0
Solid-density-type tumor	167	16	5	3	15	1

Table 4—*Relationship Between TS-CT Findings and Noguchi Type*

TS-CT Scan Findings	Noguchi Type: A	B	C	D	E	F
Air-containing-type tumor	49	53	49	0	0	1
Solid-density-type tumor	3	22	113	39	5	24

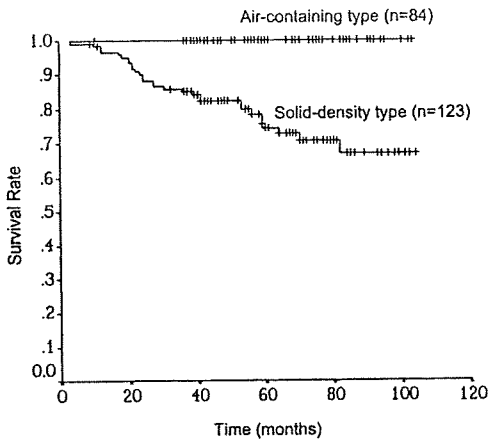

FIGURE 3. Relapse-free survival curves in patients with air-containing-type tumors and solid-density-type tumors.

metastasis, pleural invasion, vascular invasion, and lymphatic invasion, by TS-CT scan images. The parameters used to calculate the GGO ratio that have previously been reported are as follows: a GGO/tumor area ratio[5–10]; a consolidation/tumor dimension ratio[11–14]; a GGO/tumor volume ratio[15]; an area ratio of tumor on mediastinal window to that on the lung window[16,17]; a product of the dimension ratio of the tumor on the mediastinal window to that on lung window[18–20]; and a maximum dimension of tumor on the mediastinal window.[21] Matsuguma et al[8] reported on the relation between the proportion of the GGO and both clinicopathologic characteristics and tumor recurrence in patients with clinical T1N0M0 adenocarcinoma. In this study, the patients with a GGO ratio of ≥ 50% seen on high-resolution CT scans had neither lymph node metastasis nor lymphatic invasion and were alive without cancer recurrence. Ohde et al[12] reported the relation between the proportion of consolidation to GGO and pathologic invasive findings in patients with lung adenocarcinomas ≤ 3.0 cm. They showed that all tumors in which the ratio of the greatest diameter of consolidation to that of the tumor was ≤ 50% had neither lymph node metastasis nor vessel invasion and 5-year survival rate of 95.7%. Although only one cancer relapse was seen in tumors with a ratio of the greatest diameter of consolidation to that of the tumor of ≤ 50% in the study by Ohde et al[12]; the methods used to calculate the GGO ratio in these two studies[8,12] may be useful in defining noninvasive cancer. On the other hand, several investigators[16–20] used not only lung window images but also mediastinal window images to classify the tumors on TS-CT scan images. Kondo et al[16] used a ratio of the tumor area on the mediastinal window images to that on lung window images in patients with pulmonary adenocarcinoma of ≤ 2.0 cm, and showed that the tumors with a ratio of ≤ 50% had no lymph node metastasis, rare vascular invasion, and no cancer relapse. Okada et al[18] and Shimizu et al[20] used the tumor shadow disappearance rate, which was determined from the product of the maximum dimension of the tumor and the largest dimension perpendicular to the maximum axis on both pulmonary and mediastinal window images on TS-CT scan, as previously described by Takamochi et al.[22] They showed that the tumors with a tumor shadow disappearance rate of ≥ 50% had no lymph node metastasis, rare vascular invasion, and no cancer relapse in patients with lung adenocarcinomas ≤ 2.0 cm in diameter. However, the methods used to classify the tumors in these studies with both pulmonary and mediastinal window images could not completely discriminate the tumor without invasive findings (*ie*, vascular, lymphatic, and pleural involvement) from the other. In contrast, the present study showed that the air-containing-type tumor did not have lymph node metastasis, pleural involvement, vessel invasion, or lymphatic permeation, and did not recur after resection. These results suggest that the air-containing-type tumor should be defined as a noninvasive cancer.

The GGO area is sometimes neither clear nor objective. We sometimes experienced cases in which the border of consolidation and the GGO shadow on the TS-CT scan was unclear, and it was difficult or impossible to measure this size accurately. To select noninvasive cancer more simply and more objectively, we measured the maximum dimensions of tumors on both the lung and mediastinal windows. Our classification has the advantage of simplicity and objectiveness. We have only to compare the greatest dimension of the tumor on lung window images with that on mediastinal images of the TS-CT scan.

Although a number of prognostic indicators have been proposed such as TNM staging, tumor differentiation, molecular expression, and vascular inva-

Table 5—*Relationship Between Recurrence and Both TS-CT Findings and Noguchi Type Tumor in 207 Patients for Whom 3 Years or More Have Passed Since Surgery*

TS-CT Scan Findings	Recurrence		p Value
	No	Yes	
Tumors			0.000
Air-containing type	84	0	
Solid-density type	93	30	
Noguchi type tumor			0.000
Type A or B	66	0	
Type C, D, E, or F	111	30	

Table 6—*Multivariate Analysis of Relapse-Free Survival*

Variables	Hazard Ratio	95% Confidence Interval	p Value
Age	0.968	0.923–1.014	0.170
Gender (male vs female)	2.372	0.986–5.707	0.054
Tumor size	1.062	0.947–1.192	0.305
Pathologic stage (≥ II vs I)	1.795	0.598–5.389	0.297
Noguchi type tumor (type D, E, or F vs type C)	2.169	0.842–5.586	0.109
Pleural involvement (positive vs negative)	2.181	0.951–5.001	0.066
Lymphatic permeation (positive vs negative)	2.819	1.094–7.265	0.032
Vascular invasion (positive vs negative)	0.864	0.289–2.588	0.795
Operation mode (lobectomy vs wedge resection)	0.453	0.188–1.094	0.079

sion, the final results are defined only after surgery. As yet, no definite preoperative indicators have been discovered for the postoperative outcome of patients with adenocarcinomas. This study showed that preoperative TS-CT scan findings had prognostic importance. The air-containing-type tumor defined in this study showed no cancer relapse and was revealed as an independent prognostic factor for relapse-free survival. The identification of prognostic variables, especially before the operation is important to decide on the operative procedure and adjuvant therapy. Although lobectomy and pneumonectomy with systemic mediastinal lymphadenectomy is the standard surgical treatment for non-small cell lung cancer, if noninvasive lung cancers are distinguishable on CT scans, limited surgery can be indicated before the operation. Since patients with the air-containing-type tumor showed neither pathologic invasion nor relapse after surgery, we think it is reasonable that we can treat patients with lesser resection for tumors of this type. Treating patients with limited resection leads to a reduction in operative complications and the maintenance of pulmonary function. The number of both elderly patients with lung cancer and patients with a second lung cancer has been increasing. Lesser invasive techniques such as limited resection and stereotactic radiotherapy will play an important role in the future. Studies[23,24] have shown the results of the attempt to apply limited surgery for small lung tumors ≤ 2.0 cm in diameter, in which a small number of local relapses was seen in patients who underwent limited resections. Our study also showed that 11% of solid-density-type tumors had lymph node metastasis. We think that it is not the size of the tumor but the findings of the CT scan of the tumor that is a good indicator for determining whether to use limited resection. Nakata et al[25] reported the results of limited resection of pure GGO selected by the CT scan, in which no cancer relapse was seen in 33 patients who underwent limited resection. In the selection of a candidate for limited surgery, it is important to select patients with noninvasive cancers that not only have high specificity but also high sensitivity. In our study, among 162 patients with Noguchi type C tumor, which is thought to be advanced carcinoma, 49 patients had air-containing-type tumors (Table 4). This result means that our classification using TS-CT scans can preoperatively determine the presence of type C tumors without invasive findings. A prospective study is needed to clarify whether patients with air-containing-type tumors defined preoperatively on TS-CT scan images are candidates for limited surgery. In conclusion, the presence of air-containing-type tumors in patients with peripheral adenocarcinomas < 2.0 cm in diameter means noninvasive cancer and that such patients are candidates for limited surgery.

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