resection had a positive cytological result at the resection margin. The patient then underwent conversion from a limited to a standard operation, i.e. lobectomy. Thus, the patient was finally included in the lobectomy group in this study. Limited resection should be performed while maintaining a macroscopically safe surgical margin. In our institute, lesions were resected in keeping with this principle: more than 20 mm if possible, or at least with a safe margin greater than the lesion diameter under deflated condition of the lung [7]. Sawabata et al. [12] demonstrated that there were no microscopically malignant positive margins when the margin distance was greater than the maximum tumor diameter. Recently, Schuchert et al. [13] reported that a margin/tumor ratio of less than 1 is associated with a higher rate of recurrence. Lobectomy should be considered as primary therapy when such margins are not obtainable with segmentectomy in good-risk patients.

As shown in Table 4, there was no excessive resection of normal lung tissue in patients with suspected lung cancer eventually that was confirmed as benign in this study. Therefore, present management algorithm seems to be acceptable. These outcomes may indicate that invasive diagnostic approaches such as percutaneous or transbronchial lung biopsies are unnecessary for very tiny lesions or GGO lesions invisible on plain X-ray film, and surgery is indicated in tubercular or inflammatory nodules for both diagnostic and curative purposes, especially when the suspicion of cancer arises. According to the results of the Mayo Clinic low-dose spiral CT screening program for lung cancer, 1112 of 1520 participants (73%) had one or more indeterminate pulmonary nodules. Of those, 55 patients (3.6%) underwent surgery. Of those highly selected patients, 10 (18.1%) were diagnosed with benign lesions, while 45 (89.1%) were diagnosed with lung cancer [14]. In our study, 35 (19.6%) of 179 patients were determined to have benign tumors or inflammatory diseases. However, imaging techniques, including reviews of previous CT films, might allow us to determine conclusively that the lesion in question is benign [15]. It is highly likely, considering tumor doubling time, that most lesions can be identified as potentially malignant within as short a period of observation as 3–6 months. Thus, we have provided one selection arm of 'observation', especially for noncalcified lesions less than 10 mm, or pure GGO regardless of size. However, AAH and LPD produce images that are indistinguishable from BAC on HRCT. At the time of patient entry in the present study, positron emission tomography (PET) was not available in our institute. Integrated PET/CT may demonstrate an excellent performance in classifying the lesions with solid density as benign or malignant with higher sensitivity and accuracy than helical dynamic CT [16,17].

A recent revision in the World Health Organization (WHO) criteria has restricted the definition of BAC to include only those tumors with a pure alveolar growth pattern without any evidence of invasion [18]. Whether these changes will translate into actual improvements in lung cancer death rates or overdiagnosis is not yet known. We reported on noninvasive BAC showing pure GGO removed after long-term follow-up for more than 2 years. Some of these lesions were unchanged both in size and density, during the follow-up. The natural history of pure GGO is now under investigation in our department [3]. Recently, Henschke et al. [15] reported that, in modern CT screening for lung cancer at the baseline, detection of noncalcified nodules smaller than 5.0 mm in diameter does not justify immediate work-up but only annual repeat screenings to determine whether interim growth has occurred.

5. Conclusion

In conclusion, our novel treatment algorithm for small peripheral lung lesions measuring 20 mm or less in diameter, employing semiquantitative assessments of GGO area on HRCT and intraoperative lavage cytologies of resection margin of the lung as new indicators, may not only completely prevent local-regional recurrences after limited resection in cancer patients, but also avoid excessive resection of normal lung tissue in patients with noncancerous lesions. Of 21 patients with recurrences after lobectomy, 5 died more than 5 years postoperatively and 3 are alive with disease more than 5 years after surgery. In light of this evidence, we feel that long-term follow-up is necessary to collect reliable data for survival analysis, especially for tumors that exhibit slow growth characteristics such as BAC.

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Prognostic value of intraoperative pleural lavage cytology for lung cancer without carcinomatous pleuritis: importance in patients with early stage disease during long-term follow-up☆

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Abstract

Purpose: The clinical significance of intraoperative pleural lavage cytology (PLC) for lung cancer has been insufficiently elucidated. We therefore reviewed the surgical results of lung cancer patients without carcinomatous pleuritis followed up over the long term to elucidate PLC implications. **Patients and methods:** PLC was performed immediately after thoracotomy in consecutive lung cancer patients without carcinomatous pleuritis undergoing tumor resection between 1988 and 1997. Postoperative follow-up was generally performed for at least 5 years while checking tumor recurrence and survival. **Results:** Eighty-nine (13.1%) of 679 patients had positive PLC findings, which were observed more frequently in patients with advanced stage, larger tumor size, higher involvement of the pleura, lymph node, lymphatics and vessels. The overall 5- and 10-year survival rates in PLC-positive patients were 43% and 25%, respectively, while those in PLC-negative patients were 66% and 58%, respectively ($p < 0.0001$). Among 395 patients with stage I disease, 35 (8.9%) showed PLC-positive findings, and their overall survival rate was significantly poor compared with those with PLC-negative findings ($p < 0.0001$). In contrast, such differences were not observed among patients with more advanced stage diseases. In regard to histological type, a difference in the postoperative survival rate according to PLC status was statistically found in adenocarcinoma type ($p < 0.0001$), but not in squamous cell carcinoma type ($p = 0.24$). According to multivariate analysis, PLC was an independent prognostic factor for all tested patients ($p = 0.007$, hazard ratio = 0.60) as well as for those with stage I disease ($p = 0.0135$, hazard ratio = 0.51). When examining postoperative pleural recurrence, the rate for PLC-positive patients was statistically higher than that for PLC-negative patients ($p < 0.0001$, hazard ratio = 0.08). Interestingly, late pleural recurrence more than 5 years occurred in five (5.6%) of PLC-positive patients, all of whom were included in stage I. **Conclusions:** Based on the present analysis of long-term follow-up after operation, PLC may also be an independent prognostic factor. In particular, the PLC status of patients with stage I disease or adenocarcinoma type has an important impact on survival. PLC-positive findings may be a high risk for postoperative pleural recurrence. For PLC-positive patients with stage I disease, careful serial follow-up for more than 5 years is required while paying attention to late pleural recurrence.

Keywords: Lung cancer; Pleural lavage cytology (PLC); Prognosis; Pleural recurrence

1. Introduction

Despite many recent reports regarding intraoperative pleural lavage cytology (PLC) for lung cancer [1–8], the clinical significance has been undetermined in several points. First, it is considered that PLC may be a prognostic factor, but does this apply to all surgical cases of all stage diseases? [1,6] Second, PLC-positive findings may be a potential risk factor for recurrence [2,6], but the recurrence pattern has not been analyzed based on sufficiently long follow-up. Third, several investigators have shown the significance of PLC in lung adenocarcinoma [4,6,7], but how does this relate to squamous cell carcinoma of the lung? Thus, many controversial questions remain to be answered.

In our preliminary study [9], we reported the clinical importance of PLC immediately after thoracotomy and before closure of the pleural cavity for lung cancer patients without carcinomatous pleuritis. Next, we analyzed the postoperative recurrence pattern of PLC-positive patients but in these studies the follow-up periods after operation, as well as the number of patients tested, were insufficient to reach conclusions about the PLC significance [10]. Therefore, we reviewed the surgical results of lung cancer patients

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without carcinomatous pleuritis followed up for a long period, and re-analyzed the PLC implications, especially for prognosis and recurrence patterns.

2. Patients and methods

From December 1987 to December 1998, PLC was performed immediately after thoracotomy in 679 consecutive patients undergoing pulmonary resection for lung cancer without apparent findings of carcinomatous pleuritis. Patients in whom pleural dissemination or malignant effusion was intraoperatively found were excluded from the present analysis. Some of the present tested patients were included in the previously reported studies [9,10].

The method of PLC immediately after thoracotomy was previously described [9,10]. Briefly, the pleural cavity was washed with about 200 ml of physiological saline solution, most of which was then collected into a glass bottle with a mixture of heparin. After centrifugation, sediment was stained using the Papanicolaou, Giemsa and Alcian blue methods on several glass slides. The cytological results were generally classified into two categories: PLC-negative or -positive. Patients with borderline positive results, in whom a few cells with highly severe atypia or possible tumor cells (usually one or two cells) were detected in the specimen, were classified as PLC-positive.

The pathological staging was determined according to the international staging system [11], and other clinicopathological factors were quoted according to the general guidelines of the Japan Lung Cancer Society [12]. Lymphatic and vascular invasions of tumor cells were determined histopathologically, and were classified as positive and negative.

Postoperative follow-up was generally performed as follows: within 3 years after operation, systemic and local screening examinations using blood tests, chest computed tomography (CT), abdominal ultrasound echogram and bone scintigram were performed every 6 months. Brain CT or magnetic resonance imaging (MRI) was performed as needed. Between 3 and 5 years after operation, such intensive examinations were performed every year, and 5 years postoperatively; chest X-ray and blood tests were performed every year. Intensive examinations, including chest CT and abdominal ultrasound echogram, were performed when necessary. Follow-up was continued over a long period or at least more than 5 years after operation to check for tumor recurrence and survival. Survival was calculated using the Kaplan–Meier method, and differences in survival were determined by the log-rank test. Multivariate analysis of several prognostic factors was carried out using the Cox proportional hazards regression model. Zero time was the date of pulmonary resection, and the terminal event was death due to cancer or non-cancerous causes. The chi-square test was used to examine the associations between PLC results and clinicopathological factors.

3. Results

Patient clinicopathological characteristics are shown in Table 1. There were 476 men and 203 women whose ages

Table 1
Patient characteristics (n = 679).

Patient characteristics	Results (%)
Age	
<65	343 (51)
≥65	336 (49)
Gender	
Male	476 (70)
Female	203 (30)
Surgical mode	
Lobectomy	509 (75)
Bilobectomy	39 (6)
Pneumonectomy	26 (4)
Limited resection	105 (15)
Resection status	
Complete	631 (93)
Incomplete	48 (7)
Pathological stage	
IA	202 (30)
IB	191 (28)
IIA	26 (4)
IIB	98 (14)
IIIA	108 (16)
IIIB	30 (4)
IV	24 (4)
Pathological T factor	
T1	259 (38)
T2	301 (44)
T3	94 (14)
T4	25 (4)
Pathological N factor	
N0	460 (68)
N1	98 (14)
N2	113 (17)
N3	8 (1)
Tumor size	
<31 mm	323 (48)
≥31 mm	356 (52)
Pleural involvement	
P0,1	503 (74)
P2	65 (10)
P3	111 (16)
Histology	
Adenocarcinoma	408 (60)
Squamous cell carcinoma	214 (32)
Large cell carcinoma	28 (4)
Adenosquamous cell carcinoma	10 (1)
Small cell carcinoma	16 (2)
Carcinoid	3 (<1)
Histological grade	
Well	171 (25)
Moderate	328 (48)
Poor, undifferentiated	177 (26)
Unclassified	3 (<1)
Lymphatic invasion	
Positive	327 (48)
Negative	349 (52)
Not examined	3 –
Vascular invasion	
Positive	325 (49)
Negative	337 (51)
Not examined	17
Postoperative intrathoracic chemothermotherapy (PICT)	
Performed	7 (1)
Not performed	672 (99)

Table 2
PLC results and clinicopathological factors.

Factors	PLC		p value
	Positive (n = 89)	Negative (n = 590)	
Age			0.66
<65	43	300	
≥65	46	290	
Gender			0.69
Male	64	412	
Female	25	178	
Surgical mode			0.81
Lobectomy, bilobectomy	73	475	(Limited vs others)
Pneumonectomy	3	23	
Limited resection	13	92	
Resection status			0.45
Complete	81	550	
Incomplete	8	40	
Pathological stage			<0.001
I	34	359	(I vs II–IV)
II	25	99	
III	26	112	
IV	4	20	
Pathological T factor			<0.001
T1	14	245	(T1,2 vs T3,4)
T2	45	256	
T3,4	30	89	
Pathological N factor			0.024
N0	51	409	(N0 vs N1–3)
N1	16	82	
N2,3	22	99	
Tumor size			0.033
<31 mm	33	290	
≥31 mm	56	300	
Pleural involvement			<0.001
P0,1	33	470	
P2,3	56	120	
Histology			0.081
Adenocarcinoma	58	350	(Adenocarcinoma vs squamous cell carcinoma)
Squamous cell carcinoma	20	194	
Others	11	46	
Histological grade			0.68
Well, moderate	67	432	(Well, moderate vs poor, undifferentiated)
Poor, undifferentiated	22	155	
Unclassified	0	3	
Lymphatic invasion			0.031
Positive	52	275	(Positive vs negative)
Negative	36	313	
Not examined	1	2	–
Vascular invasion			<0.001
Positive	55	270	(Positive vs negative)
Negative	28	309	
Not examined	6	11	
Postoperative intrathoracic chemothermotherapy (PICT)			
Performed	7	0	
Not performed	82	590	

ranged from 21 to 87, with a median of 64 years. The resected tumors ranged from 5 to 140 mm, with a median of 31 mm.

Eighty-nine (13.1%) of 679 patients had positive PLC findings. Table 2 shows an association between PLC-positive findings and clinicopathological factors. Positive PLC findings were observed more frequently in patients with more advanced T factor (T1,2 *vs* T3,4, $p < 0.001$), N factor (N0 *vs* N1–3, $p = 0.024$) and stage (I *vs* II–IV, $p < 0.001$), larger tumor size (smaller than 31 mm *vs* larger than 30 mm, $p = 0.034$), greater involvement of the pleura (P0,1 *vs* P2,3, $p < 0.001$), and more aggressive lymphatic (negative *vs* positive, $p = 0.031$) and vascular (negative *vs* positive, $p < 0.001$) invasion. As for histological type, positive PLC findings were observed marginally more frequently in patients with adenocarcinoma type, in comparison with squamous cell carcinoma type ($p = 0.082$).

Because of intraoperative PLC-positive findings, postoperative intrathoracic chemothermotherapy (PICT) was selectively performed for seven patients within the period. This therapeutic modality was previously described in detail by Kodama et al. [13,14].

Among the 342 surviving patients in the database top, 58 (17.0%) were lost to follow-up during the initial 5-year postoperative period, but the rest (83.0%) could be followed up for more than 5 years. The median follow-up period for all patients was 6.7 years, ranging from 0.5 month to 19.6 years. The overall 5- and 10-year survival rates in all patients in the present series were 62% and 51%, respectively. The overall 5- and 10-year survival rates in PLC-positive patients were 43% and 25%, respectively, while those in PLC-negative patients were 66% and 58%, respectively ($p < 0.0001$) (Fig. 1A). Among 393 patients with stage I disease, 34 (8.7%) showed PLC-positive findings, and their 5- and 10-year overall survival rates were 57% and 33%, respectively, which was significantly poor compared with those with PLC-negative findings (80% and 68%, $p < 0.0001$) (Fig. 1B). However, these clear differences

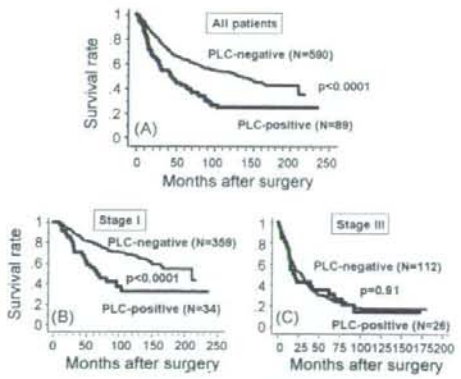

Fig. 1. Overall survival curves according to intraoperative PLC status: stage-based analysis. (A) All tested patients, (B) patients with stage I (IA + IB) disease, (C) patients with stage III (IIIA + IIIB) disease. The overall survival curves of all tested patients and those with stage I disease are shown in parts A and B. PLC-positive patients showed significantly poorer prognosis than those with PLC-negative findings (all patients: $p < 0.0001$, those with stage I disease: $p < 0.0001$); however, such prognostic significance disappeared in patients with stage III disease (C).

Table 3
Univariate and multivariate analysis results for prognosis-associated factors.

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
All patients				
PLC (Neg. vs Pos.)	0.50 (0.38–0.66)	<0.0001	0.60 (0.44–0.82)	0.001
Age (<65 vs >65)	0.80 (0.64–0.99)	0.037	0.75 (0.60–0.94)	0.013
Gender (male vs female)	1.52 (1.19–1.95)	0.001	1.34 (1.01–1.78)	0.044
Surgical mode (non-limited vs limited)	1.61 (1.16–2.24)	0.005	0.82 (0.60–1.19)	0.23
Complete (yes vs no)	0.34 (0.25–0.48)	<0.0001	0.50 (0.35–0.73)	<0.001
p stage (I vs II–IV)	0.28 (0.23–0.35)	<0.0001	–	
T factor (T1,2 vs T3,4)	0.47 (0.37–0.60)	<0.0001	0.87 (0.59–1.29)	0.50
N factor (N0 vs N1–3)	0.29 (0.23–0.36)	<0.0001	0.41 (0.31–0.53)	<0.001
Tumor size (<31 vs >31 mm)	0.53 (0.43–0.66)	<0.0001	0.72 (0.56–0.94)	0.014
Pleural involvement (P0,1 vs P2,3)	0.49 (0.39–0.61)	<0.0001	0.90 (0.63–1.29)	0.57
Histology (adeno. vs non-adeno.)	1.42 (1.15–1.77)	0.001	1.02 (0.79–1.32)	0.87
Histological grade (well, moderate vs poor)	0.65 (0.52–0.62)	0.0002	0.80 (0.63–1.02)	0.074
Lymphatic invasion (Neg. vs Pos.)	0.42 (0.34–0.52)	<0.0001	0.75 (0.57–0.99)	0.040
Vascular invasion (Neg. vs Pos.)	0.41 (0.33–0.52)	<0.0001	0.67 (0.52–0.87)	0.020
Patients with stage I disease				
PLC (Neg. vs Pos.)	0.41 (0.26–0.62)	0.0002	0.57 (0.33–0.97)	0.039
Age (<65 vs >65)	0.52 (0.36–0.74)	0.0003	0.61 (0.42–0.88)	0.008
Gender (male vs female)	1.52 (1.04–2.23)	0.031	1.18 (0.76–1.82)	0.47
T factor (T1 vs T2)	0.45 (0.32–0.65)	<0.0001	0.50 (0.27–0.92)	0.026
Tumor size (<31 vs >31 mm)	0.59 (0.42–0.82)	0.021	1.34 (0.74–2.37)	0.31
Pleural involvement (P0,1 vs P2)	0.58 (0.35–0.97)	0.037	1.02 (0.54–1.93)	0.96
Histology (adeno. vs non-adeno.)	1.74 (1.23–2.45)	0.002	1.38 (0.91–2.09)	0.13
Lymphatic invasion (Neg. vs Pos.)	0.71 (0.49–1.01)	0.055	0.98 (0.47–1.44)	0.93
Vascular invasion (Neg. vs Pos.)	0.42 (0.30–0.59)	<0.0001	0.49 (0.34–0.71)	<0.001

disappeared as the disease stage progressed; the difference in the overall survival rate was $p = 0.10$ among patients with stage II disease, $p = 0.91$ with stage III disease (Fig. 1C), and $p = 0.40$ with stage IV disease, respectively. According to univariate analyses, all the listed 14 clinicopathological factors, age, gender, surgical mode, resection status, T factor, N factor, stage, tumor size, pleural involvement, histology, histological grade, lymphatic and vascular invasions and PLC findings had a statistical influence on the postoperative prognosis (Table 3). According to multivariate analyses using 13 prognosis-associated factors, except for stage (Table 3), age, gender, resection completeness, N factor, tumor size, lymphatic or vascular invasions, or PLC finding were independent prognostic indicators in all the tested patients. As for patients with stage I disease, 9 factors, age, gender, T factor, tumor size, pleural involvement, histology, lymphatic and vascular invasions, and PLC findings were potential prognosis-associated factors according to univariate analyses (Table 3).

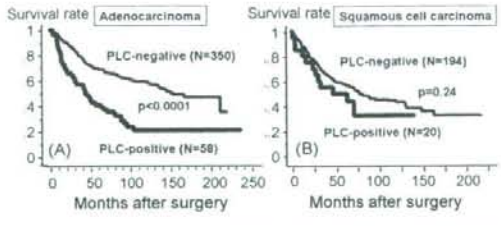

Fig. 2. Overall survival curves according to intraoperative PLC status: Histology-based analysis. (A): Adenocarcinoma, (B) squamous cell carcinoma. Whereas PLC findings for patients with adenocarcinoma had a significantly strong impact on survival ($p < 0.0001$), those for squamous cell carcinoma lacked prognostic value ($p = 0.24$).

Multivariate analyses showed that age, T factor, vascular invasion and PLC findings were independent prognostic indicators in this population. According to the prognostic analysis of PLC based on histological type, while PLC findings for patients with adenocarcinoma have a strong impact on survival, they are lacking in prognostic value for squamous cell carcinoma. While 5- and 10-year overall survival rates of PLC-positive patients with adenocarcinoma were 42% and 22%, respectively, which was significantly worse than those with PLC-negative findings (72% and 71%, $p < 0.0001$), the survival rates of PLC-positive patients with squamous cell carcinoma were 53% and 34%, respectively, in comparison with PLC-negative patients (59% and 48%, $p = 0.24$) (Fig. 2A and B).

Regarding the tumor recurrence pattern among PLC-positive patients, distant metastases (32/89, 36.0%) were more commonly observed rather than local recurrence (24/89, 27.0%); however, it was important that 21 (23.5%) of the PLC-positive patients also showed postoperative pleural recurrence, which were observed in only 14 (2.4%) of PLC-negative patients. In addition, based on Kaplan–Meier analysis only regarding pleural recurrence as the event, the difference was also significant (Fig. 3, $p < 0.0001$, hazard ratio = 0.08, 95% CI = 0.04–0.15). It was noted that, whereas the rate of pleural recurrence more than 5 years after operation was only 0.3% (2/590 patients) among PLC-negative patients, such a late recurrence occurred in five (5.6%) of the PLC-positive patients, all of whom had stage I disease, and surprisingly, two of whom showed a very late recurrence after more than 10 years of follow-up. Among seven patients undergoing PICT, three showed local pleural recurrence, as shown by arrows in Fig. 3. Of five patients with late pleural recurrence, two patients had been treated with PICT.

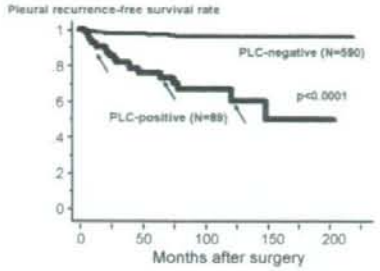

Fig. 3. Pleural recurrence-free survival curves according to PLC status. Patients with PLC-positive findings showed pleural recurrence more frequently than those with PLC-negative findings ($p < 0.0001$, hazard ratio = 0.08, 95% CI = 0.04–0.15). Late pleural recurrence 5 years after surgery was observed in five patients (5.6%) among PLC-positive patients. Arrows show pleural recurrence among PLC-positive patients undergoing postoperative intrathoracic chemothermotherapy (PICT) [13,14].

4. Comments

In the present study, we conducted postoperative follow-up for a long period, at least for more than 5 years, and obtained clinical information about recurrence and survival regarding the loco-regional pleural cavity. As a result, postoperative follow-up could be performed for more than 80% of surviving patients. In contrast, follow-up periods in many previously published reports were only 5–7 years [1–6,9], and such data may be insufficient to conclude the clinical significance of PLC. In fact, it is important that late pleural recurrence more than 5 years after surgery occurred in a minority of PLC-positive patients.

PLC status in patients undergoing surgical treatment for lung cancer is widely accepted to be a powerful prognosis-associated factor, as reported previously by many investigators [1–9], some who showed that it was an independent prognostic indicator by multivariate analyses [2–4,8]. In contrast, according to our preliminary report [9], PLC status immediately after thoracotomy was statistically lacking in prognostic value, although it univariately influenced post-operative survival. In the present study using many patients for long-term follow-up, its prognostic value was clearly demonstrated.

Thus, it can surely be concluded that PLC status has an important value in prognosis, at least for surgically treated patients, but interestingly, it was noted that its prognostic significance was limited in patients with rather early stage diseases. Namely, a difference in the PLC status effect on survival in patients with stage I disease was statistically observed, while it was not seen in those with stage III disease. In patients with stage II disease, the p value was marginally 0.098. Similar data have been previously reported by several investigators [1,2,6,7], but this study may be the first to describe clearly that the prognostic implication of PLC was found only among patients with early stage (stage I) disease. In contrast, considering that the PLC-positive rate is closely correlated with tumor progression-associated markers such as T factor, N factor, tumor size, pleural involvement, lymphatic and vessel invasion, the prognostic significance of the PLC status gradually disappeared in more advanced stage disease.

In addition, it is interesting that the prognostic significance of PLC was observed in adenocarcinoma, not in squamous cell carcinoma. Also, it was noted that the PLC-positive rate was marginally different between these histological types. The difference in PLC significance by histology has been pointed out by several investigators [1,2,4,6], but the reason is still unknown. We speculate that such a difference is owing to some differences in the biological and oncological characteristics between these two representative histological types. In our previous report [9], the number of cell clusters in the PLC solution was important for the postoperative clinical course, and there were generally fewer in the PLC solution in squamous cell carcinoma than in adenocarcinoma. Thus, PLC had little clinical significance in patients with squamous cell carcinoma, but the histological difference of prognostic significance should be re-evaluated using a larger group of patients.

When examining the postoperative recurrence site, distant metastases were commonly observed even among PLC-positive patients (36%). Considering the clinical findings of the PLC status in relation to tumor progression and poor prognosis, distant metastases were easily regarded as the major pattern of tumor recurrence among PLC-positive patients [2], in particular those with advanced stage disease. On the other hand, positive PLC findings in patients have been described as reliable information for potential carcinomatous pleuritis by many investigators [2,6,9,10]. The rate of pleural recurrence among such PLC-positive patients was considered to be 15–35%. We also reported preliminarily that pleural failure occurred in 17 (18%) of 97 PLC-positive patients and, in this series, the rate was as high as 23.5%. Moreover, we should pay attention to the timing of pleural recurrence. In the present study, it was noted that 5.6% of PLC-positive patients showed late pleural failure more than 5 years after operation and, to our surprise, very late pleural recurrence after more than 10 years occurred in two patients. Importantly, all patients showing such late or very late local recurrence in the pleural cavity had stage I disease. Therefore, for PLC-positive patients with stage I disease, long-term follow-up may be strongly required, especially focusing on local pleural recurrence. In other words, while systemic therapy should be planned for PLC-positive patients with advanced stage disease, local control therapy is also required for those with early stage disease. In our institute, PICT has been aggressively performed for selected patients with pleural dissemination [13,14] and, recently, its application was preliminarily expanded for PLC-positive patients with stage I or II disease. In the present series, only seven patients underwent this therapeutic modality, but the clinical effect has been not evaluated because of the small number. Several investigators have reported the possible usefulness of intrapleural hypotonic cisplatin therapy during operation [6,15,16]. Satoh et al. [6] emphasized that such local therapy may not be sufficient for prognosis improvement, but we think that a local therapeutic modality should be established as the first step for selected PLC-positive patients.

In conclusion, according to the present analysis of long-term follow-up after surgery, PLC immediately after thoracotomy for lung cancer may be an independent prognostic factor, especially for patients with stage I disease

or adenocarcinoma. PLC-positive findings may indicate a high risk of pleural recurrence. Importantly, for PLC-positive patients with stage I disease, serial careful follow-up for more than 5 years is necessary while paying attention to late pleural recurrence.

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Topics

肺がんCT検診認定技師制度について

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1．背景と目的

日本放射線技術学会ではスーパーテクノロジスト認定制度委員会[1, 2]：CT専門技師認定班（井田義宏班長：藤田保健衛生大学）の下でCT領域における専門技師制度の検討が行われている．CT専門技師認定班のなかでは軸であるCT専門技師と並行して，低線量肺がんCT検診（以下，CT検診）に特化した肺がんCT検診認定技師制度に関する検討も行われている．ここでは後者の肺がんCT検診認定技師（以下，CT検診認定技師）[3]について述べる．

CT検診認定技師制度は本学会を含む6学会*1が参加した肺がんCT検診合同認定検討委員会（長尾敬一委員長：千葉大学，2007年発足）のなかで，肺がんCT検診認定医（以下，CT検診認定医）とともに検討が行われ，制度の実現化に向けて検討が進んでいる．また認定機構の本年度内の設立に向けて準備が行われている．CT検診認定医は本年5月に日本胸部外科学会総会において第1回の暫定講習会が開催され，以後，各学会において講習会が開催される予定である．後者のCT検診認定技師に関しては被ばく低減技術と装置の安全管理，そして読影医の支援として1次スクリーニングを行える能力の担保が求められる．このためCT検診認定技師の養成には講習会などを通じた専門的なトレーニングと，その後に行う認定試験が計画されている．

肺がんCT検診認定制度の目的は以下にある．

1）CT検診を通じて肺がんの早期発見，早期治療を行うことで日本国民の肺がん死の低減に寄与する．
2）検診に伴う受診者の被ばく低減を行い，また装置の安全管理と精度管理を行うことで安全なCT検診を普及させる．
3）認定制度を通じて検診施設間の質のばらつきをなくし，同時に検診施設の水準を上げることでCT検診全体の質を担保する．
4）CT検診における高度な画像の標準化を図り，認定医との協力体制の下で読影支援を行う．
5）CT検診の合理的評価のために全国統一的なCT検診データベース*2を通じて，有効性評価のためのデータ収集に努める．
6）人の認定と施設認定の設立を基にがん対策基本法に基づく肺がん死の低減法としてのCT検診普及の必要性と検診に対する変革を訴える．

以上の6つである．CT検診分野において認定制度を通して人材を確保することで，多くの国民がそのニーズに応じて，いつ，どこの施設でも，安全で精度の高いCT検診を受けることができる体制を構築していくことが目的である．

2．肺がんCT検診認定技師の業務内容（案）

CT検診におけるCT検診認定技師の役割は，①撮影業務，②装置の安全管理，③受診者情報管理，④線量（被ばく低減）管理，そして⑤1次スクリーニングの5つである．

2-1　撮影業務

検診分野では多くの健常者が対象となる．このために受診者のX線被ばくを最小限にしつつ，検診のための読影に適した最適なスキャンパラメータによる撮影[4–6]が必須の業務となる．これには画像情報を最大限に引き出すためのスキャンデータに対する画像処理も含まれる．

2-1-1　シングルスライスCT（single slice CT：SSCT）を用いた検診において

一定の大きさの肺結節に対してスキャン終了後，そ

*1日本医学放射線学会，日本呼吸器外科学会，日本呼吸器学会，日本CT検診学会，日本肺癌学会，日本放射線技術学会の6団体．
*2低線量CTによる肺癌検診のあり方に関する合同委員会 編「低線量CTによる肺癌検診の手引き」金原出版，東京，2004にCD-ROMで添付されている肺癌CT検診業務支援総合データベースなど．

の場で高分解能CT(以下，high resolution CT：HRCT)を実施する．これにより要精査受診者の再来院などに伴う負担軽減を行い読影精度と検診能率の向上を図っていく．ここでは得られたCT画像に対し異常所見の検出を行い，的確にHRCTを実施できる能力が要求される．この場合に受診者に対してTSCT(thin section CT)の実施に伴う被ばくを過度に与えることのないように基礎解剖に基づいた十分な肺疾患に対する知識，および撮影技術を持つことが要求される．

2-1-2 マルチスライスCT(multi slice CT：MSCT)を用いた検診において

検診現場のMSCTでは1～2.5mm前後の撮影スライス厚でデータ収集された後，5～10mm厚の画像スライス厚として再構成され読影[7,8]されることが多い．この場合に結節の存在を的確に判断しスキャン終了と同時に，結節に対する拡大処理を含む1～2mm厚前後のHRCT画像を作成し，また必要に応じて任意断面画像の作成と生データ(投影データ)の保存*1など画像処理を行う能力が要求される．これによりMSCTのスキャン情報を有効に生かすためのスキャンデータの運用が可能となり，MSCTの性能を最大限に生かした診断情報の高いCT画像を読影医に提供することができる．これらの業務は既に多くの検診施設で行われている(土屋班：全国検診施設アンケート調査より)．しかしその判断基準は施設，担当技師により異なるのが現状である．この課題に対しCT検診認定技師により，これらの業務を全国統一的な基準で行うことで，常に読影医に対して最良の撮影技術に対応した最高の画像情報を提供していかなければならない．

2-2 装置の安全管理と精度管理，線量(被ばく)管理

多くの検診施設ではCT装置は1台であり代替装置はない．CT装置を安全と精度管理を通して装置の稼働率と信頼性を維持しながら，CT装置の性能を最大限に発揮させることは必須な業務となる．同時に，最小限の被ばく線量で肺結節を検出するための最適スキャン条件の設計，画像描出条件，線量管理などの環境整備を行っていく．

2-3 1次スクリーニングとしての異常所見の拾い上げ

今後，予想される検診施設と受診者数の増加，MSCTに代表される膨大な画像データは読影医に対し過度な負担となり，読影能率と検診能率を低下させる．これに対して画像データに対して異常所見の検出を行うことにより読影医(CT検診認定医)の負担を軽減し，検診能率を向上させていく．ただしこの業務は医師の監督下でのみ，行われることが前提となる．また，そのための専門的トレーニングによる肺解剖と疾患，読影に関する十分な基礎知識の習得が行われることが必須条件となる．

3．スクリーニング業務とCT検診認定技師としての要件

3-1 スクリーニングを行うためのminimum requirement

スクリーニングを行うためには2つの必要条件がある．1つは1次スクリーニングの業務はCT検診認定医師の下でのみ行われなければならないことである．第2には，CT検診認定技師における1次スクリーニングの業務は肺に関する解剖と疾患，読影に関する専門的なトレーニングを受け，基礎知識を十分に習得した後，認定試験に合格した技師が担当することである．CT検診認定技師が行う1次スクリーニングの業務は施設の状況に応じて決められるべきものである．十分な数の読影医(CT検診認定医)が存在し，読影業務が負担なく行うことができる施設ではCT検診認定技師は被ばく低減と撮影業務が主となる．医師の確保と医師間の2重読影が困難であり，また読影業務がCT検診認定医に対して過度な負担となる施設においてはCT検診認定医との十分な協議の下にCT検診認定技師による1次スクリーニングが検討されるべきである．現在，日本CT検診学会においてCT検診認定技師の有効性評価に関する読影実験[9-11]が行われている．

CT検診認定技師が行ったスクリーニング結果を読影医側に伝える手段としては，a)フイルムを用いてCT画像の異常所見に対して赤鉛筆などでマーキングを行う方法，b)専用の読影画像ビューアーを用いてマーキングする方法*2，c)CAD[12]を用いる方法，d)報告用紙に検出結果を記載し，またキー画像を貼り付ける方法などが提案されている．検診CT画像の判定にはCT検診認定技師は関与しない．また医師側は1次スクリーニングが行われた画像に対して，もう一度すべての画像をチェックすることが求められる．しかし検診CT画像に対して1次スクリーニングが事前に行われることで医師の読影業務の負担は従来に比べ，はるかに軽減され，検診能率と精度を向上させることができる．重要なことはCT検診分野に従事する放射線技師のスキルを活用し，スキル・ミックス(skill-mix)を行うなか

*1ディスク内の生データ容量には制限がある．再構成画像と異なり，生データはスキャンの繰り返しにより上書きされ消去される．HRCTに必要な拡大再構成，高分解能関数処理は生データに対して再構成処理を行うことで得られる．
*2肺がんCT検診認定技師のマーキングした結節の座標を記録し，2次読影の際に参照表示できるビューアーシステム．現在，新潟大学(和田真一研究室)，放射線医学総合研究所(松本　徹)，富士通の共同研究にて開発中である．

で読影業務の能率を向上させ，CT検診全体の効率化を行うことでCT検診を安全に，精度よく，実用的な検診手段として全国的に普及させることである．

3-2 CT検診認定技師としてのminimum requirement

CT検診認定技師は専門的トレーニングを受けた後，以下の能力を習得していることを必要条件とする．能力の有無は筆記および読影試験により行われ，定められた成績と感度を持つことが要求される．

1)10mm以上の大きさを持つ結節の確実な拾い上げ
2)5～9mmの大きさの結節の拾い上げ(一定の感度で)
3)被検者に合った最適なスキャン条件による検査を行う能力
4)受診者の被ばく管理と被ばく低減を行える能力
5)受診者情報保護・管理の能力

4．肺がんCT検診認定技師養成のための教育研修(案)

4-1 Web，CDを利用した受講準備システム

講習会(教育研修)はこれを受講し，その内容を修得することで肺がんCT検診認定技師に必要な解剖・疾患に関する知識，そして業務を行うために必要な肺結節に対する検出基準に達することが前提となる．このためには，いかに講習会を能率よく行うかが課題となる．このためには講習会の前に時間をかけての自己学習が必須条件となる．この課題に対して，Web，CDを利用したティーチングファイル*1が準備されている．これらを講習会受講前に十分に学習することで肺がんCT検診認定技師の肺結節に対する検出能力を短時間で目標レベルに到達させることが可能と考える．

4-2 講習会案

講習会は2日間を想定している．肺がんCT検診認定技師の受講科目の内容のなかで基礎項目の習得はWeb，CDで講習会の受講前に終え，講習会では存在診断に関するトレーニングに重点を置く．また2日目の最終に認定試験と読影試験を実施し，肺結節の検出能力が目標としている感度に達しているか否かの試験を行うことが計画されている．この計画に対しては平成18年度には斎藤班の小班として，読影能力試験を想定した駒沢大学IT教室(50台のパソコンとサーバーのローカルエリアネットワークシステム)にて，保健学科学生と診療放射線技師の合計25名にて検診CT画像の読影認定試験のシミュレーションが実施され，どのように肺がんCT検診認定技師の読影能力を認定するのかの検討が行われた(Fig. 1)．

Fig. 1 専用画像ビューアーを用いた肺がんCT検診の読影認定試験のシミュレーション実験

5．肺がんCT検診認定技師の実現に向けての課題

制度の実現に向けた今後の課題として，その有効性の評価と効果的な教育方法，認定制度準備委員会の設置，技術力の向上などがある．第1の肺がんCT検診認定技師の存在を保証するエビデンスとして，専門的なトレーニングを受けた肺がんCT検診認定技師は，実際に肺がんCT検診画像を読影している医師と比較し，結節の存在診断において差がないということの証明が必要となる．この課題に対しては2007年2月の第14回日本CT検診学会において，土屋班研究結果として柿沼らは，5mm以上のpure ground-glass opacity (GGO)やmixed GGOの結節や，6mm以上の充実型の結節の存在診断において有意差がないことを報告している．第2の効果的な教育方法については講習会の受講，インターネット上での教育ソフトでの自己学習などの前と後での結節検出能に関する比較実験などを通じての学習効果に関する検討が必要となる．

今後，肺がんCT検診認定技師制度が真に役立つ制度となるためにはCT検診認定医側はCT検診認定技師に対してCT画像から必要最低限のどのような所見を読み取り，どのようなレポートが欲しいのか，具体的な要求が必要となる．それに対してCT検診認定技師側は医師からの要求に応えられるように1次スクリーニングのための具体的な方法と得られる結果を医師と

*1①「新しい検診モデルの構築と検診能率の向上に関する研究」班作成：ティーチングファイルとテキスト．②学術調査班研究報告：肺癌検診用MDCT，SSCT撮影マニュアル作成班研究報告，日放技学誌，2007．III低線量ヘリカルCTによる肺がん検診の読影教育用ソフトウェア"ALCA Project-The Simulation"．③厚生労働科学研究費補助金．土屋班：Low-dose Helical CT Screening for Lung Cancer using Multislice CT：NCC Projectなど．

ともに検討し，十分な協力体制による読影力向上を図ったうえで実務に入ることが必要となる．さらにCT検診認定技師およびCT検診認定医の技術向上のために，結果をフィードバックする施設内および精検施設，治療施設との合同カンファレンスの設置，あるいは精度管理への積極的な参加が行われる体制を作ることが必要と考える．また臨床的に緊急な対応を要する病態の存在を検出した場合のCT検診認定医に対する連絡体制のルールの検討も必要となる．

6．まとめ

低線量肺がんCT検診は日本が世界に先駆けて行った画期的な早期肺がん発見のためのシステムであり，日本はこのCT検診を幅広く，安全に，実用的なレベルで実施するための体制を構築しなければならない．このためにはCT検診分野において人材確保必須な条件となる．CT検診はその対象の多くが健常者となる．このために受診者ごとの最適スキャン条件による被ばく線量の低減と最大の画像情報を有したCT画像の読影医側への提供，そしてCT画像上の異常所見の検出(1次スクリーニング)を通しての読影医への支援が必要となる．CT検診認定技師制度は今後のCT検診の普及の鍵を握る制度と考える．

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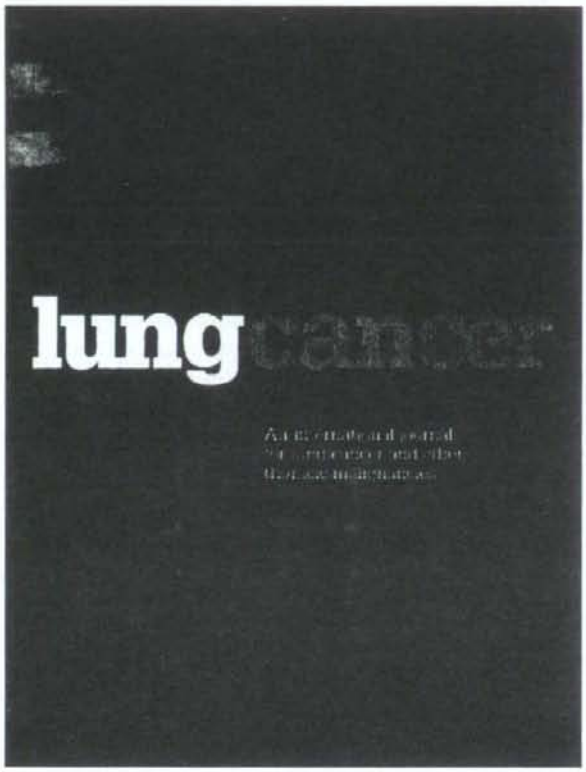

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Lung cancer screening—Comparison of computed tomography and X-ray

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Lung cancer;
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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

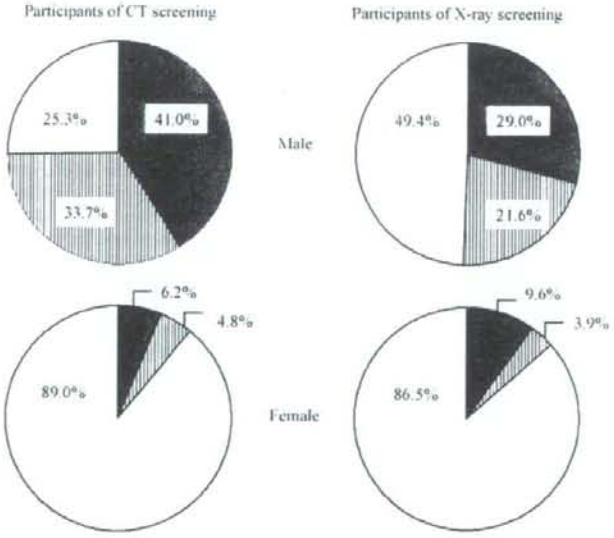

Fig. 1 Smoking status of the participants in the 2 screening programs. Closed, shaded and open areas represent current, ex- and never smokers, respectively. Smoking rates of the participants in the X-ray screening were similar to the general statistics in Japan, in both male and female populations, whereas 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

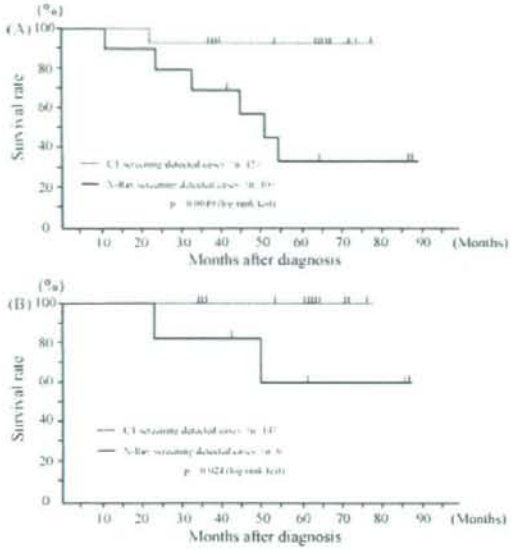

Fig. 2 Survival curves of patients with lung cancer according to screening method. Patients detected by CT screening ($n = 15$) survived significantly longer than patients detected by X-ray screening ($n = 10$, A). Comparison between the 2 groups limited to the subpopulations undergoing surgery showed 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.