Japanese Society of Thoracic Radiology

A Case of Malignant Pleural Mesothelioma With Osseous and Cartilaginous Differentiation

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Abstract: A 69-year-old man with a history of exposure to asbestos was admitted because of a chest radiographic abnormality. Subsequent findings from computed tomography and a thoracoscopic biopsy suggested malignant mesothelioma. Punctate calcification was observed in the pleural tumor on computed tomography scanning. The patient underwent pleuropneumonectomy, and the tumor was pathologically diagnosed as malignant mesothelioma, sarcomatoid type with osseous and cartilaginous differentiation. Malignant mesothelioma with osseous and cartilaginous differentiation is a rare condition. Punctate calcification in the pleural mass as a lesion distinct from the pleural plaque may indicate osseous or osteosarcomatous differentiation in malignant mesothelioma.

Key Words: malignant pleural mesothelioma, osseous differentiation, cartilaginous differentiation, computed tomography, calcification

(*J Thorac Imaging* 2011;26:W30–W32)

Malignant pleural mesothelioma is a rare primary tumor of the pleura. It is macroscopically classified as localized or diffuse type, and histologically divided into epithelioid, sarcomatoid, desmoplastic, and biphasic types according to the World Health Organization Classification of Tumours, 2004.[1]

Osseous and/or cartilaginous differentiation is an extremely rare presentation in malignant mesothelioma. Osteosarcomatous lesions that appear as dense, punctate calcified foci on computed tomography (CT) scans are rarer still, and only a few cases have been reported.[2–5] Here, we report a case of malignant pleural mesothelioma with osseous and cartilaginous differentiation, in which dense, punctate calcifications were observed on CT scanning.

CASE REPORT

A 69-year-old man who had no significant past medical history was admitted to the department of thoracic surgery. Five months before admission, the patient was asymptomatic but had an abnormal chest radiograph. Results from a subsequent CT scan and thoracoscopic biopsy suggested the diagnosis of malignant mesothelioma. The patient was a building contractor and had been exposed to asbestos for 48 years. There were no significant findings on physical examination. Findings from laboratory tests and tumor markers, including carcinoembryonic antigen, cytokeratin fragment, cancer antigen 19-9, and pro-gastrin-releasing peptide, were within normal range; however, levels of neuron-specific enolase and squamous cell carcinoma antigen were slightly elevated.

Chest x-ray revealed an approximately 10-cm mass with clear margins in the right middle hemithorax and a smaller caudal mass (Fig. 1). In addition, right-sided pleural thickening was observed. CT scanning revealed masses contiguous with the right pleura, and dense, calcified foci were detected in the main tumor (Fig. 2). The calcifications were punctate and uniform (largest diameter, 5 mm) and were diffusely scattered throughout the tumor. Linear calcification also appeared in the pleural plaque. In the lung window setting, the right lung parenchyma was compressed by the pleural tumors, but no tumors were observed within the right lung parenchyma or the left hemithorax. There was no evidence of pulmonary fibrosis.

Right pleuropneumonectomy was performed with chest wall resection. Macroscopic examination revealed multiple nodules and tumors, which arose from the parietal pleura. The largest tumor, which was yellowish white and 9 cm in diameter with clear margins, compressed the right lung adjacent to the tumor (Fig. 3A). Calcifications could be palpated in the tumor and pleura.

Histologic examination revealed a solid growth pattern with oval-to-elongated spindle cells (Fig. 3B). Osteosarcomatous components were scattered in the tumor nests (Fig. 3C), and focal chondrosarcomatous components were observed. Although the tumor invaded the lung parenchyma, most of the tumor grew in the parietal and visceral pleurae. Immunohistochemical examination revealed atypical spindle cells that expressed positive mesothelioma

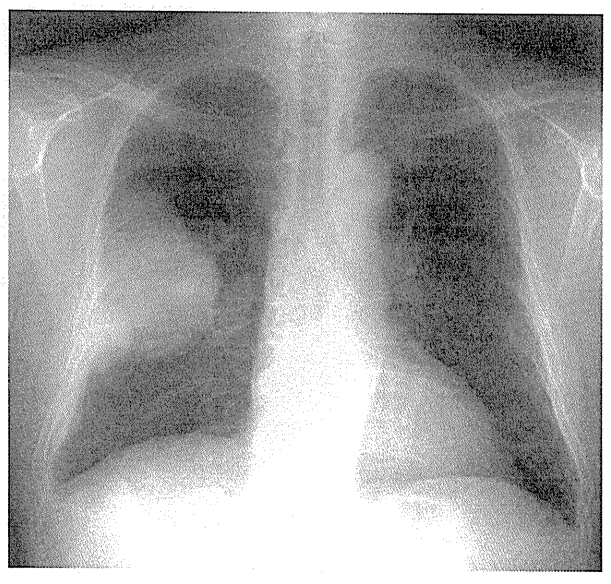

FIGURE 1. Chest radiograph showing well-defined tumor masses in the right hemithorax.

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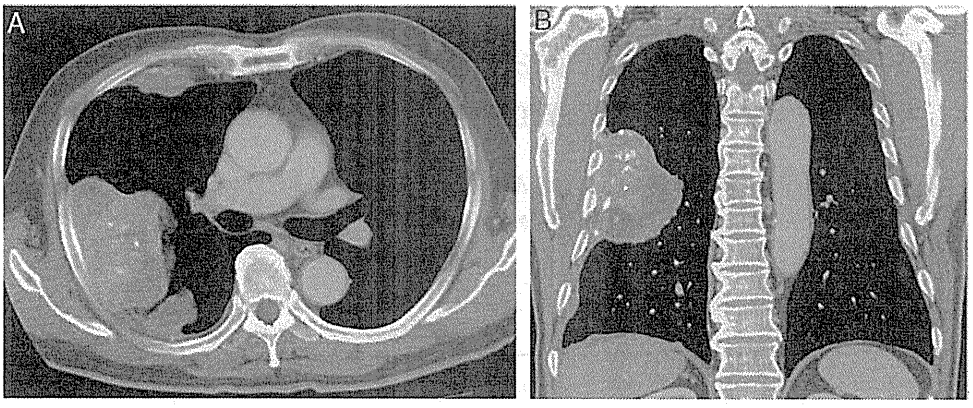

FIGURE 2. A, Axial contrast-enhanced CT scan of the thorax showing masses in the right pleura. Punctate calcifications were detected in the main tumor. B, Coronal reformatted image clearly shows that the tumor arises from the pleura.

markers (calretinin, podoplanin, and Wilms tumor-1), but did not express negative mesothelioma markers (carcinoembryonic antigen, thyroid transcription factor-1, and Ber-Ep4). Asbestos bodies were detected in the lung parenchyma. On the basis of these findings, we diagnosed malignant pleural sarcomatoid mesothelioma with osseous and cartilaginous differentiation.

The patient developed both local recurrence and metastasis and died 19 months after surgery.

DISCUSSION

Malignant pleural mesothelioma is a rarely encountered, high-grade malignant primary tumor. Cases among men have declined in the United States[6]; however, the incidence is increasing in Japan.[7] Development of osseous or cartilaginous differentiation in malignant mesothelioma is very rare, and Goldstein first reported 2 cases in 1979.[8] He suggested that the pluripotentiality of coelomic mesothelium may be the cause of its differentiation toward bone and cartilage, and also proposed the following alternative hypotheses: (1) the cartilage and bone, developed separately from the neoplasm, could be caused by previous tuberculous pleurisy; (2) the mesothelioma might have produced a substance that promoted cartilage and bone formation, directly or by stimulating the parathyroid glands; (3) the cartilage and bone might be integral components of the neoplasm and in parts the spindle cells might be merging or transforming into the cartilage; (4) 2 separate neoplasms may have been present, a mesothelioma with classical tubular formation and a fibrochondrosarcoma; and (5) asbestotic pleural plaques often undergo calcification.

Bolen et al[9] demonstrated the process by which subserous connective tissue cells obtained epithelial characteristics. They suggested that the pathogenesis is caused by the multipotency of mesothelial cells, using the term multipotential subserosal cells, which supports the hypothesis of pluripotent coelomic mesothelium proposed by Goldstein.[8] Yousem and Hochholzer[10] also favored this hypothesis. Our case supports this hypothesis, as there was no evidence of tuberculosis infection or other primary

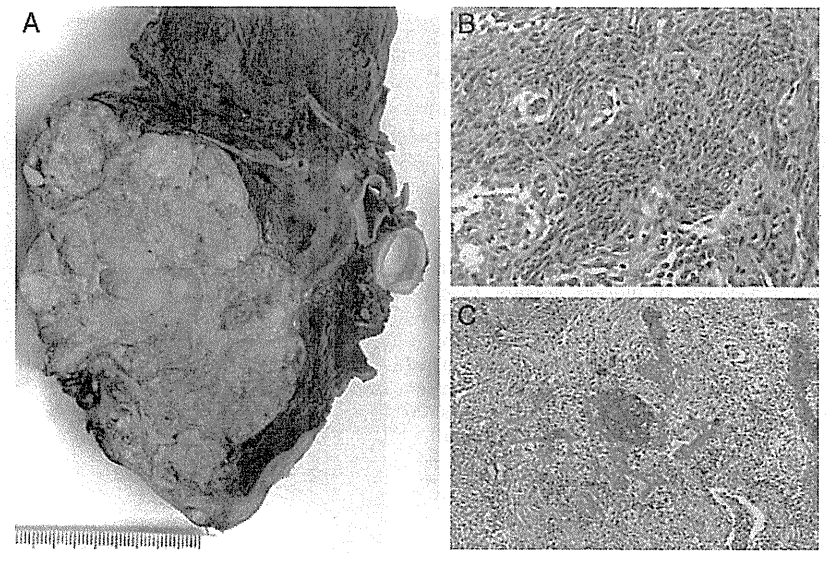

FIGURE 3. A, The cut surface of the largest tumor. The tumor has a diameter of 9 cm, is composed of yellowish white nodules with focal ossification, and is compressing the right lower lobe of the lung. B, Sarcomatoid mesothelioma shows oval-to-elongated spindle cells. C, Irregular-shaped osteoid components with calcium deposition are observed in the nests.

tumors and the osseous lesion was not colocalized with asbestos plaque. However, the possibility of parathyroid hormone influence cannot be excluded.

Of the 2 cases reported by Goldstein,[8] one case showed osteosarcomatous differentiation, and the other showed bone and cartilage differentiation. Sonja et al[11] summarized 27 cases of malignant mesothelioma with heterologous elements. In their report, they suggested that the term "heterologous" should be reserved for tumors that show malignant heterologous elements, such as osteosarcomatous, chondrosarcomatous, or rhabdomyoblastic elements. Pathologically, the differential diagnosis of these cases includes a primary or secondary pleural sarcoma. They concluded that mesothelioma cannot be excluded if cytokeratin staining is negative and should be diagnosed by anatomic distribution. The prognosis after diagnosis of mesothelioma with heterologous elements is similar to that associated with pleural mesothelioma of the sarcomatoid type; survival is approximately 6 months. Our case included heterologous elements such as osteosarcomatous and chondrosarcomatous differentiation.

Several reports have described imaging findings of pleural mesothelioma, but only 3 reports mentioned tumor calcifications detected by CT scanning.[2–5] Arnold et al[2] reported 2 cases of diffuse malignant mesothelioma that presented with large and dense calcified pleural masses, which were visualized on CT scan. In this report, it was described that the diagnosis of osteocartilaginous differentiation in diffuse malignant mesothelioma was based on the past history of asbestosis exposure, the typical radiographic appearance of encasing pleural tumor, the histopathologic features of malignant mesothelioma, and the absence of any osteogenic sarcoma or chondrosarcoma elsewhere. In this case, large calcification inside the main tumor was not seen, but punctate calcification was evident on CT scanning. Calcification of benign pleural plaque and osseous differentiation in mesothelioma could be distinguished by their shape and location. Calcification of benign pleural plaque is linear and is located on thickened pleural plaque, whereas osseous differentiation in mesothelioma is punctate or large and is located inside the tumor. The radiologic differential diagnoses of malignant pleural tumor with calcification include lung cancer with pleural dissemination, sarcoma derived from pleura, and metastatic lung or pleural tumor, such as colorectal cancer, osteosarcoma, and chondrosarcoma.

In conclusion, we report a case of malignant mesothelioma with osseous and cartilaginous differentiation. The punctate calcifications in the pleural tumor, distinct from the pleural plaque, may indicate osseous or osteosarcomatous differentiation in malignant mesothelioma.

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Lung Cancer 67 (2010) 318–324

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The adenocarcinoma-specific stage shift in the Anti-lung Cancer Association project: Significance of repeated screening for lung cancer for more than 5 years with low-dose helical computed tomography in a high-risk cohort☆

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ARTICLE INFO

Article history:
Received 20 January 2009
Received in revised form 25 April 2009
Accepted 27 April 2009

Keywords:
Stage shift
Size shift
Repeated screening
Low-dose helical computed tomography
High-risk cohort
Invasive lung adenocarcinoma

ABSTRACT

Background: We investigated whether a stage shift occurs during long-term repeated screening for lung cancer with low-dose helical computed tomography (LDCT) in a high-risk cohort.
Methods: A total of 2120 subjects (mean age, 63 years; 87% male and 83% smokers) were continuously recruited and underwent repeated screening with LDCT from 1993 through 2004.
Results: Nineteen lung cancers were detected at baseline examinations (prevalence cancers), and 57 lung cancers were detected at subsequent examinations (incidence cancers). For both prevalence cancers and incidence cancers, adenocarcinoma (74% and 63%, respectively), especially invasive adenocarcinoma (42% and 23%, respectively), was the most common histological diagnosis, and stage IA was the most common pathological stage (58% and 79%, respectively). The detection rate of incidence cancers other than bronchioloalveolar carcinoma became significantly higher after 5 years of LDCT examinations ($r=0.50$, $P=0.020$). Moreover, both the percentage of cancers of stage II–IV and tumor size became significantly lower for invasive adenocarcinoma after 5 years of LDCT examinations ($r=-0.77$, $P=0.007$ and $r=-0.60$, $P=0.029$, respectively).
Conclusions: Repeated screening for more than 5 years might demonstrate the efficacy of LDCT screening for lung cancer through an adenocarcinoma-specific stage shift.

1. Introduction

Lung cancer is considered as an appropriate disease for screening because it is the leading cause of cancer death worldwide, symptomatic disease is generally lethal, localized disease can be managed curatively, and high-risk cohorts can be defined on the basis of tobacco consumption [1]. However, screening with chest X-ray films or sputum cytological examination has failed to reduce lung-cancer mortality rates in randomized, controlled trials [2–6].

Low-dose helical computed tomography (LDCT) is a promising screening method because a higher percentage of asymptomatic, X-ray–invisible, or stage IA lung cancers (mostly adenocarcinoma) are found with baseline or repeated computed tomography (CT) examinations than with conventional screening methods [7–11]. In fact, according to the results of the International Early Lung Cancer Action Program, the 10-year survival rate for all patients with lung cancer was 80% regardless of stage or treatment [12]. If the cancer was in clinical stage I and was promptly resected, the 10-year survival rate was 92%. However, because large, randomized, controlled trials of LDCT screening are still in progress [13,14], whether LDCT screening reduces lung-cancer mortality rates remains uncertain. Although mortality data are needed to determine whether LDCT screening is effective, indirect evidence for a possible mor-

Abbreviations: CT, computed tomography; LDCT, low-dose helical computed tomography; BAC, bronchioloalveolar cell carcinoma; ALCA, Anti-lung Cancer Association.

☆ This work was presented as an oral presentation at the 42nd Annual Meeting of the American Society of Clinical Oncology, 2006, Atlanta, GA.

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0169-5002/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2009.04.016

tality reduction can be obtained from a "stage shift," an increase in the detection rate of putatively curable early-stage lung cancers and a concomitant decrease in incurable late-stage cancers, leading to a decrease in the lung-cancer-specific mortality rate [15], which can be used as a surrogate endpoint even in a nonrandomized, uncontrolled trial.

Results of many single-armed, uncontrolled trials of annual screening with LDCT have been published [12,16–22]. However, none of these trials has documented a stage shift, perhaps because the number of lung cancers detected with repeated screening was too small (range, 4–35 cancers) or because the duration of repeated screening (range, 1–4 years) was too short. Thus, to determine whether a true stage shift occurs, a longer-term LDCT study with a larger number of detected lung cancers is required.

Furthermore, studies performed to date have not considered the effect of histological classification on the stage shift. Recent LDCT trials suggest that an increase in early-stage lung cancer might not be accompanied by a decrease in late-stage lung cancer (i.e., overdiagnosis) [15] and that the presence of localized bronchioloalveolar cell carcinoma (BAC) and mixed adenocarcinoma with BAC component might reflect overdiagnosis bias, although adenocarcinoma without BAC component behaves as aggressively as do other non-small cell carcinomas [23].

In the present study, on the basis of an update of the Anti-lung Cancer Association (ALCA) project [16], we investigated whether a stage shift occurs when lung cancers are stratified by histological subtype during long-term repeated LDCT screening for lung cancer in a high-risk cohort comprising mostly male smokers in their 60s.

2. Patients and methods

2.1. Study population

From September 1993 through August 2004, LDCT screening was performed semiannually by the ALCA in Tokyo. The ALCA is a for-profit organization established in 1975 to thoroughly screen for lung cancer in dues-paying participants. Because the participants are continuously recruited from members of the general population 40 years or older with a history of smoking (>20 pack-years) or a single episode of hemoptysis within the past 6 months, most participants are male smokers in their 60s. Written informed consent was obtained from each participant at baseline CT screening.

2.2. Screening procedures

Screening was performed as described previously [16]. Briefly, at baseline screening a simple questionnaire about smoking history and symptoms was completed, and LDCT, chest radiography (posterior–anterior position), and sputum cytological examination pooled for 3 days were performed. Participants were invited twice a year by mail after the baseline screening to repeat the same screening procedures. The CT scanner (TCT-900S Superhelix, Toshiba Medical, Tokyo, Japan) was used under the following conditions: 120 kVp, 50 mA, 10-mm collimation, 1 rotation of the X-ray tube per second, and a table speed of 20 mm/s (pitch, 2:1). Image construction was performed with 180° linear interpolation at 1-cm intervals. All CT images were examined by 2 of 7 readers (radiologists or thoracic physicians).

2.3. Evaluation of detected lung cancers

The staging and the histological classification of detected lung cancers were performed according to the International System for Staging Lung Cancer [24] and the World Health Organization lung tumor classification system [25], respectively. Cancers were classified as adenocarcinoma, squamous cell carcinoma, other non-small cell carcinoma, or small cell carcinoma. Moreover, adenocarcinoma was subclassified on the basis of the histological growth pattern as localized BAC, mixed adenocarcinoma with BAC component, and adenocarcinoma without BAC component (invasive adenocarcinoma).

Lung cancers detected at baseline screening were considered "prevalence cancers," whereas those newly detected at subsequent repeated LDCT screening examinations were considered "incidence cancers." Furthermore, lung cancers diagnosed outside our semiannual LDCT screening procedure within a screening interval were defined as "interval cancers," whereas those diagnosed outside our screening procedure after a period longer than the screening interval (due to refusal by ALCA participants) were not classified as "interval cancers." The presence or absence of interval cancers was confirmed through questionnaire when participants were invited twice a year by mail after the baseline screening to repeat the same screening procedures.

Excluded from analysis were 6 cases of hilar lung cancer detected on sputum cytological examinations or on evaluation of hemoptysis but not with LDCT.

2.4. Statistical analysis

Statistical *P* values for the differences in percentages and means were evaluated with the χ^2 test and the *t*-test, respectively. Survival curves were estimated with the Kaplan–Meier method, with survival time defined as starting from when microscopic evidence for malignancy was first obtained to the date of death or November 25, 2005, whichever came first. Differences in survival rates between groups were evaluated with the log-rank test. Multivariate Cox proportional hazards model analysis was performed to identify significantly independent prognostic factors for overall survival. Linear regression analysis with the least-squares method was performed for the relationships between groups. All calculations were performed with Stat View 5.0J software (SAS Institute Inc., Cary, NC). *P* values less than 0.05 were considered to indicate statistical significance.

3. Results

3.1. Characteristics of participants

During the study period, 20,113 LDCT scans were performed for 2120 ALCA participants (mean age, 63 years; 87% male and 83% smokers), and 76 peripheral lung cancers were detected. Participants underwent LDCT screening a median number of 7 times (range, 1–22 times; Fig. 1A); a median number of 3 lung cancers were detected in each ordinal screening (range 0–9; Fig. 1B); a median of 3.5 years had passed since a participant's baseline screening (range, 0–10.5; Fig. 1C); and a median of 0.5 years had passed since a participant's previous screening (range, 0–10.0; Fig. 1D). Of the 2120 ALCA participants, 243 (11%) underwent only baseline LDCT screening, 753 (36%) underwent repeated LDCT screening for more than 5 years, and 322 (15%) underwent repeated LDCT screening for more than 10 years.

3.2. Comparison of results between baseline and subsequent LDCT screenings

The characteristics of all participants and of participants who underwent at least 1 subsequent LDCT screening examination are shown in Table 1. No significant difference was observed between these groups in terms of age, sex, or smoking status at baseline. However, the detection rate of lung cancer was significantly higher

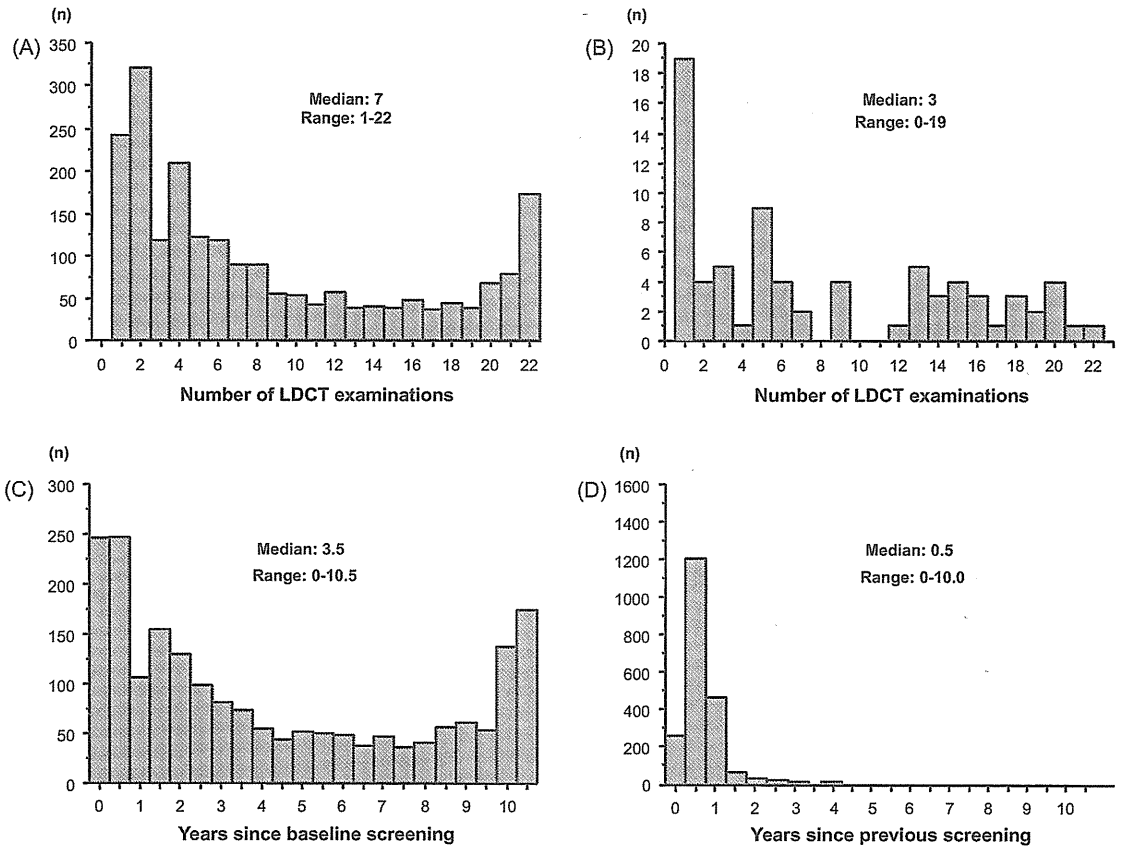

Fig. 1. Characteristics of repeated LDCT screening. (A) Distribution of the number of times participants underwent repeated LDCT screening (*X* axis indicates the number of LDCT examinations, and *Y* axis indicates the number of participants in each ordinal screening). (B) Distribution of the number of lung cancers detected in screening examinations grouped by ordinal number (*X* axis indicates the number of LDCT examinations, and *Y* axis indicates the number of lung cancers detected in each ordinal screening.). (C) Distribution of years since participants had undergone baseline screening (*X* axis indicates years since baseline screening, and *Y* axis indicates the number of participants in each ordinal screening period). (D) Distribution of years since participants had undergone previous screening (*X* axis indicates years since previous screening, and *Y* axis indicates the number of participants in each ordinal year since previous screening).

at baseline screening (0.90%: 19 prevalence cancers in 2120 participants) than at repeated screenings (0.32%: 57 incidence cancers in 1877 participants; $P<0.001$).

The characteristics of 76 patients with lung cancers detected at screening examinations are summarized in Table 2. The 19 patients with prevalence cancers and the 57 patients with incidence cancers did not differ in age, sex, or smoking status. However, both the percentage of positive chest X-ray films (53% vs. 16%, $P=0.004$) and tumor size (24 mm vs. 17 mm, $P=0.018$) were significantly less in patients with incidence cancers than in patients with prevalence cancers. Although neither histological diagnosis nor pathological stage differed significantly between patients with prevalence cancers and those with incidence cancers, in both groups of patients adenocarcinoma (74% and 63%, respectively), especially invasive adenocarcinoma (42% and 23%, respectively), was the most common histological diagnosis and stage IA was the most common pathological stage (58% and 79%, respectively).

Table 1
Characteristics of participants.

	Baseline LDCT	Repeated LDCT	*P*
No. of participants	2120	1877	
Age (years, mean ± SD)[a]	63 ± 11	64 ± 11	NS
Sex (% male)	87	88	NS
Smoking (% smokers)[a]	83	84	NS
No. of detected lung cancers	19	57	
No. of screenings	2120	17993	
Detection rate (%)	0.90	0.32	<0.001

[a] Fixed at baseline screening.

Survival rates were compared between patients with prevalence cancers and those with incidence cancers. The 5- and 10-year survival rates were 84.5% and 84.5%, respectively, in patients with incidence cancers ($n=57$) and were 68.7% and 38.1%, respectively, in

Table 2
Clinicopathological characteristics of patients with screening-detected lung cancer.

	Prevalence cancers	Incidence cancers	*P*
No. of patients	19	57	
Age (years, mean ± SD)[a]	66 ± 8	69 ± 9	NS
Sex (% male)	84	86	NS
Smoking (% smokers)[a]	89	93	NS
Positive X-ray (%)	53	16	0.004
Tumor size (mm, mean ± SD)	24 ± 15	17 ± 10	0.018
Histological type			NS
Adenocarcinoma	14 (74%)	36 (63%)	
BAC	2	11	
Adenocarcinoma with BAC	4	12	
Invasive adenocarcinoma	8	13	
Squamous cell carcinoma	4	12	
Other non-small cell carcinoma	1	5	
Small cell carcinoma	0	4	
Pathological stage			NS
IA	11 (58%)	45 (79%)	
IB	2	3	
II	0	3	
III	5	4	
IV	1	2	

BAC: bronchioloalveolar cell carcinoma.
[a] Fixed at baseline screening.

patients with prevalence cancers ($n = 19$). No significant difference was observed between the groups (log-rank test, $P = 0.208$). Multivariate analysis with the Cox proportional hazards model found that only pathological stage ($P = 0.006$) was an independent prognostic factor for overall survival. The risk of death in patients with stage II–IV disease was increased 8.26-fold (95% confidence interval, 1.85–37.03). In contrast, age, sex, smoking status, tumor size, histological subtype (presence of BAC component), and screening type (baseline vs. repeated) were not independent prognostic factors.

No interval lung cancers were detected outside our semiannual LDCT screening procedure within a screening interval. However, 3 lung cancers were detected outside our screening procedure after a period longer than the screening interval. For these 3 lung cancers, the histological classification and stage, screening period from baseline to previous screening, and time since previous screening, respectively, were: invasive adenocarcinoma, stage IV, 5 years, and 4 years; squamous cell carcinoma, stage IA, 3.5 years, and 5 years; and other non-small cell carcinoma, stage II, 5 years, and 1.5 years.

3.3. The presence of an increased detection rate, a stage shift, and a size shift

The detection rate of all 57 incidence cancers was positively correlated with the duration of repeated screening ($r = 0.50$, $P = 0.020$) but remained uncorrelated if the duration of repeated screening was 5 years or less (Fig. 2A). In contrast, the detection rate of localized BAC showed a weak negative correlation with the duration of repeated screening ($r = -0.38$, $P = 0.086$). Other histological subtypes, including invasive adenocarcinoma, showed no significant correlations.

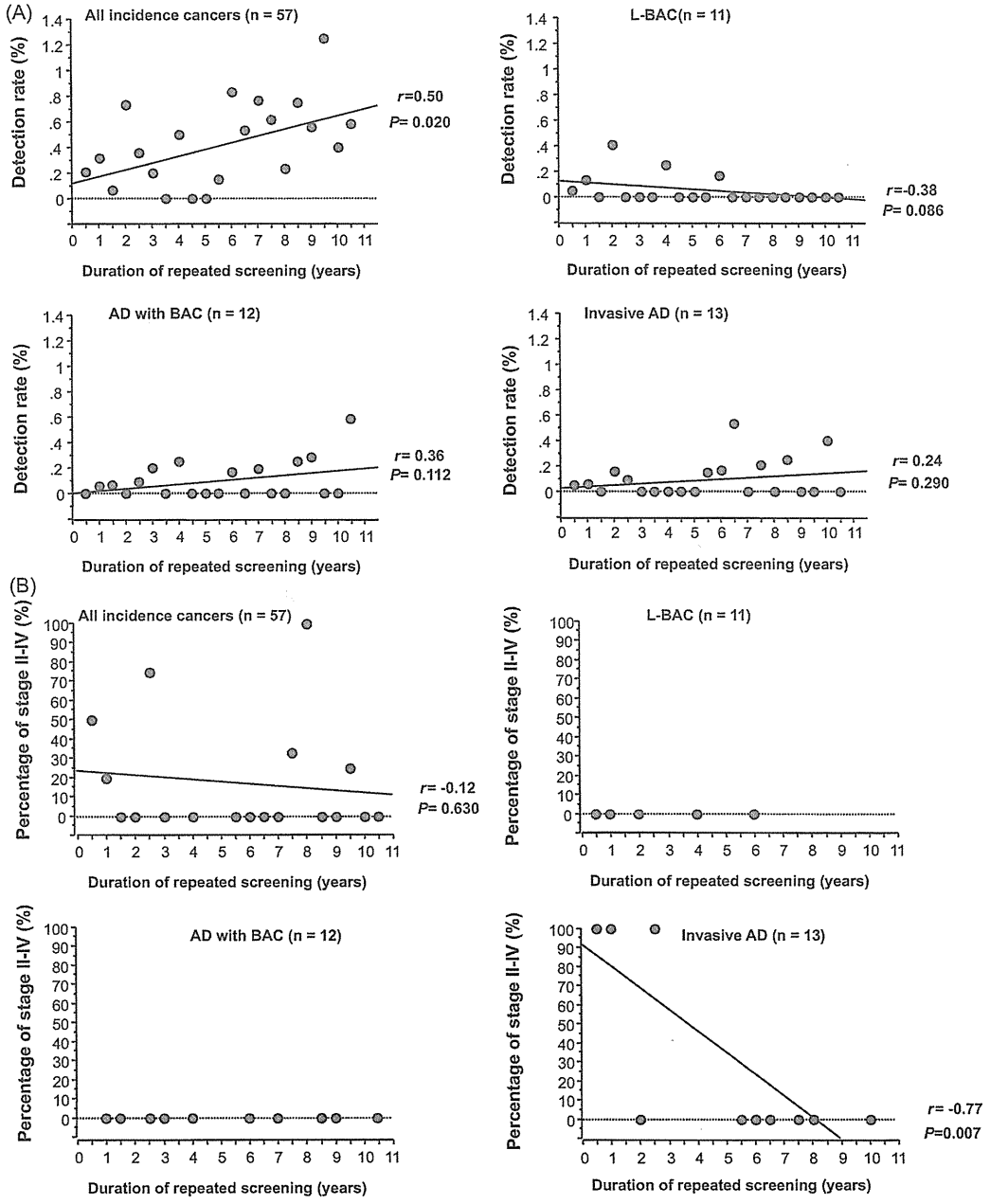

Fig. 2. Relationship between the duration of repeated screening and characteristics of incidence lung cancers. Correlations between the duration of repeated screening and the detection rate (A), the proportion of stage II–IV disease (B), and tumor size (C) were evaluated according to histological subtypes. L-BAC, localized bronchioloalveolar carcinoma; AD, adenocarcinoma.

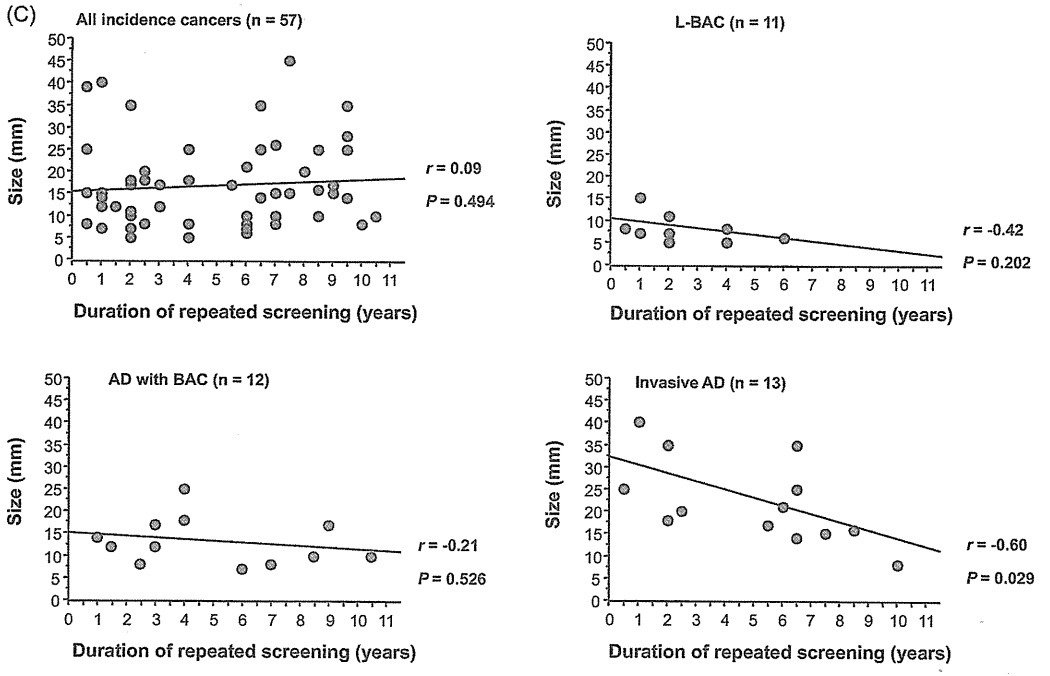

Fig. 2. (*Continued*).

Although the percentage of stage II–IV disease among all 57 incidence cancers was not correlated with the duration of repeated screening ($r=-0.12$, $P=0.630$), the percentage of stage II–IV disease among invasive adenocarcinoma was negatively correlated with the duration of repeated screening ($r=-0.77$, $P=0.007$) but remained uncorrelated if the duration of repeated screening was 5 years or less (Fig. 2B). In contrast, the percentage of stage II–IV disease among both localized BAC and mixed adenocarcinoma with BAC component remained 0% regardless of the duration of repeated screening. Neither squamous cell carcinoma ($r=-0.12$, $P=0.767$) nor small cell carcinoma ($r=-0.67$, $P=0.999$) showed a significant correlation between the percentage of stage II–IV disease and the duration of repeated screening.

Similarly, although tumor size among all 57 incidence cancers was not correlated with the duration of repeated screening ($r=-0.12$, $P=0.630$), the tumor size of invasive adenocarcinoma was negatively correlated with the duration of repeated screening ($r=-0.60$, $P=0.029$) but remained uncorrelated if the duration of repeated screening was 5 years or less (Fig. 2C). In contrast, other histological subtypes showed no significant correlations.

4. Discussion

In the present study involving 10 years of semiannual LDCT screening in a continuously recruited cohort comprising mostly male smokers in their 60s, increased detection rates were observed for lung cancers other than localized BAC. Moreover, both a stage shift and a size shift were observed for invasive adenocarcinoma of the lung. This report is, to our knowledge, the first to document the significance of long-term repeated screening for lung cancer with LDCT in a high-risk cohort.

Recently, Bach et al. have demonstrated that screening for lung cancer with LDCT may not meaningfully reduce the risk of advanced lung cancer or death from lung cancer [26]. Their conclusion was based on a model predicting deaths from lung cancer applied to 3 studies of LDCT screening in asymptomatic population at risk for lung cancer [20–22]. However, most importantly, the screening period of each of the 3 studies was less than 5 years. If each screening period had been 5 years or longer, Bach et al. might have instead confirmed a decrease in the lung-cancer-specific mortality rate. The screening period is important for other cancers for which the efficacy of screening has already been demonstrated; for example, the period of screening with fecal occult blood for colorectal cancer has been shown to be the important factor in a large randomized, controlled trial [27]. The initial protocol of the study specified 5 years of screening; however, the Policy and Data Monitoring Group recommended that screening be reinstituted because of the lack of statistical power regarding the mortality rate through 5 years of screening in the population. Screening then continued for 10 years, resulting in the finding of a lower mortality rate in screened subjects. Furthermore, meta-analysis of 8 randomized, controlled trials of screening mammography has demonstrated a statistically significant reduction in mortality rate among women aged 40–49 years at entry through screening for 10 years [28]. In particular, in 1 of these studies, the mortality rate from breast cancer was similar in screened group and the control group during the first 8 years but then became lower in screened group after 8 years [29]. Therefore, the efficacy of repeated screening for lung cancer might be demonstrated only with a long screening period.

To determine whether LDCT screening can reduce the mortality rate from lung cancer, a large, randomized, controlled trial has been started in the United States (National Lung Screening Trial) [13]. In this trial, 50,000 subjects at high risk for lung cancer were randomly assigned to undergo screening with chest radiography or LDCT at baseline and then annually for 2 additional years with annual telephone follow-up thereafter. Accrual was completed in February 2004, and final analyses are scheduled to be completed in 2009. In addition, a Dutch-Belgian randomized trial (NELSON trial) comparing CT screening with no screening at baseline and then 2 repeated screenings within 3 additional years in almost 20,000 subjects at high risk for lung cancer should be completed by 2010 [14]. However, if only long-term, repeated LDCT screening produces a stage shift, these 2 trials of short-term, repeated LDCT screening might fail to show any benefit. In fact, we should note that the detection rate of incidence lung cancers of all types remained unchanged if the duration of repeated screening was 5 years or less. Furthermore, neither a stage shift nor a size shift in invasive adenocarcinoma occurred if the duration of repeated screening was 5

years or less. Therefore, considering our present findings that the detection rate of incidence lung cancers in a cohort of mostly male smokers increased after 5 years of repeated LDCT screening and that the stage shift was observed for at least invasive adenocarcinoma after long-term, repeated LDCT screening for 5 years, we believe that proving the efficacy of LDCT screening would be difficult if the screening period is less than 5 years.

In the present study both a stage shift and a size shift were observed for invasive adenocarcinoma of the most common histological diagnosis. Considering direct evidence exists for a stage-size relationship in LDCT screen-diagnosed lung cancers [30], the fact that the stage shift was followed by a simultaneous size shift supports the occurrence of a stage shift in invasive adenocarcinoma. However, we wonder why this phenomenon was observed for only invasive adenocarcinoma. This question is difficult to answer, considering that invasive adenocarcinoma behaves as aggressively as do other non-small cell carcinomas. A possible explanation might simply be that the number of incidence lung cancers detected in our study lacks sufficient statistical power. However, some adenocarcinomas have higher volume-doubling times, grow more slowly, and are, therefore, diagnosed more easily at an early stage; another explanation could be length-time-biased sampling inherent to single-armed, uncontrolled trials. Thus, large, randomized, controlled trials on the basis of long-term repeated screening will be necessary to answer this question.

In the present study, we have performed semiannual LDCT screening to detect aggressive, fast-growing lung cancers at an early stage. However, no interval lung cancers were detected in our screening population. On the other hand, an interesting phenomenon is shown by the characteristics of 3 patients with lung cancers detected outside our screening procedure after a period longer than the screening interval. These lung cancers were detected after the patients had stopped undergoing semiannual LDCT screening because no abnormality was observed during the screening periods, which were 3.5 years in 1 patient and 5 years in 2 patients. Therefore, these facts suggest the efficacy of long-term repeated LDCT screening for more than 5 years.

We have several concerns about our study. The first concern is that, in addition to the stage shift caused by long-term repeated screening, we estimated the efficacy of long-term repeated screening could also be shown indirectly if the overall survival of patients with incidence cancers would be significantly longer than that of patients with prevalence cancers. So, we compared baseline screening with subsequent screening. However, multivariate Cox proportional hazard model analysis showed that the screening type (baseline vs. repeated screening) was not an independent prognostic factor for overall survival. A possible reason for this finding is the small number of participants and, therefore, the small number of deaths from lung cancer in both groups. Thus, larger studies involving larger numbers of participants are needed to investigate whether the overall survival of patients with incidence cancers is, in fact, significantly longer than that of patients with prevalence cancers because of the efficacy of long-term repeated screening. A second concern is that the partial-volume effect might affect the ability of screening CT images to demonstrate small nodules because only thick-section screening CT with image construction at 1-cm intervals was available during the screening period. Therefore, in a second ALCA study still in progress we have performed both chest radiography and LDCT to evaluate the detection power of LDCT in terms of the partial-volume effect. A third concern associated with long-term semiannually repeated LDCT screening is that a large number of healthy persons would be exposed to radiation and have an increased risk of radiation-induced lung cancer, although the risk of radiation-induced cancers other than lung cancer would be far lower [31,32]. According to one estimate, LDCT screening at a rate of 1.5 examinations per year would induce 4.5 lung cancers per year in 100,000 persons aged 60–70 years [33]. According to another estimate, annual LDCT screening would induce approximately 6.7 lung cancers per year in 100,000 persons if male current smokers aged 60 years undergo annual screening until age 75 years with a compliance rate of 50% [34]. In contrast, because our population with a median age of 64 years undergoes LDCT screening twice a year, the risk of radiation-induced malignancy would be slightly higher. However, assuming that our semiannual screening yielded 57 lung cancers in 1877 participants during a median follow-up period of 3.5 years, the yearly incidence of lung cancer in 100,000 participants would be 868. Furthermore, because the 13 incidence invasive adenocarcinomas detected with the benefits of a stage shift and a size shift in our study suggest an incidence of 198 cancers per year per 100,000 persons, which is far larger than that of radiation-induced lung cancers, we maintain that semiannually repeated LDCT screening is beneficial despite the potential harm of the radiation exposure.

In conclusion, we have demonstrated that both a stage shift and a size shift occur for invasive lung adenocarcinoma during long-term repeated LDCT screening in a high-risk cohort. Long-term repeated screening for more than 5 years might disclose the potential efficacy of LDCT screening for lung cancer as the truth has been disclosed for other types of cancers, including colorectal cancer and breast cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Cancer Research (17-2) from the Ministry of Health, Labor, and Welfare of Japan, and supported in part by a Grant-in-Aid for the Third-term Comprehensive 10-Year Strategy for Cancer Control (Category: Japanese General Screening Study for Asbestos-related Diseases) from the Ministry of Health, Labor, and Welfare of Japan.

We thank the physicians and technical staff of the ALCA.

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≪肺癌診療の基礎知識≫

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江口研二　太田修二　関　順彦

特集　肺癌生存期間延長の謎――今何が起こっている？

臨床雑誌「内　科」第103巻　第2号〔2009年2月号〕別　刷

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肺癌診断のこつと画像診断における最近の話題

江口研二　太田修二　関　順彦*

要旨

- CTで発見される小型肺癌が増え，Ⅰ期肺癌切除例の割合が増加している．
- 肺癌全体では過半数が進行癌で発見され，早期診断は大きな課題である．
- 重喫煙者（喫煙指数：1日の本数×年数＞600），血痰などは，肺門部肺癌の高危険群であり，X線写真だけでなく喀痰細胞診が必要である．
- 肺野型肺癌には，喀痰細胞診は無効であり，X線画像で小型の異常陰影を発見することがもっとも重要である．
- 血液腫瘍マーカーは早期肺癌診断には役に立たないが，組織型の補助診断および高値例では，治療後の再発モニタリングに有用である．
- 神経症状や骨病変による疼痛などが初発症状となる肺癌はまれでなく，50歳以上の喫煙者などで頑固な増悪する上記症状を有する場合は，一度胸部CTを勧める．
- CT，MRI，PET/CTなどの診断機器の進歩は著しいが，適切な検査法を選択する必要がある．

はじめに

厚生労働省人口動態統計（2006年）によると，癌による死亡者数は年間32万人に上り，肺癌はもっとも多く年間死亡者数が6万人を超えている．男性肺癌死亡率は，人口10万人対74人で癌腫の中で第1位である．女性では（人口10万人対26人），胃癌に次いで癌死亡率の第2位である[1]．本邦における喫煙率は，男性39%，女性11%（2005年）で，欧米に比べ依然として高率である．肺癌一次予防としての禁煙対策は，厚生労働省の「健康日本21」施策でも，公共の場および職場での分煙徹底，禁煙支援プログラムの受診普及，未成年喫煙の廃絶を掲げているが[2]，現状は改善の兆しがない．2007年に策定された国のがん対策推進計画でも，喫煙に関する数値目標は削除されてしまった．

CTで発見される小型肺癌が増えたため，専門医療機関ではⅠ期肺癌切除例の割合が増加している．しかし高齢化社会では，肺癌患者数は増加しており，依然として，過半数の症例は進行癌で発見されている．早期発見の必要性は大きな課題である．

肺癌の臨床区分，症状，診断手順（Fig. 1）

1．肺癌の臨床区分[3,4]

肺癌は，その発生部位から肺門部肺癌（三次気管支までに発生）と肺野型肺癌（末梢の細気管支肺胞領域に発生）に区別すると，臨床的な診断・治療の考え方がわかりやすい．肺門部肺癌は，発生場所が太い気道（管腔）なので，早期症例では，胸部X線写真では腫瘍自体は認められず，気管支の狭窄などによる二次性の閉塞性肺炎像が発見動機とな

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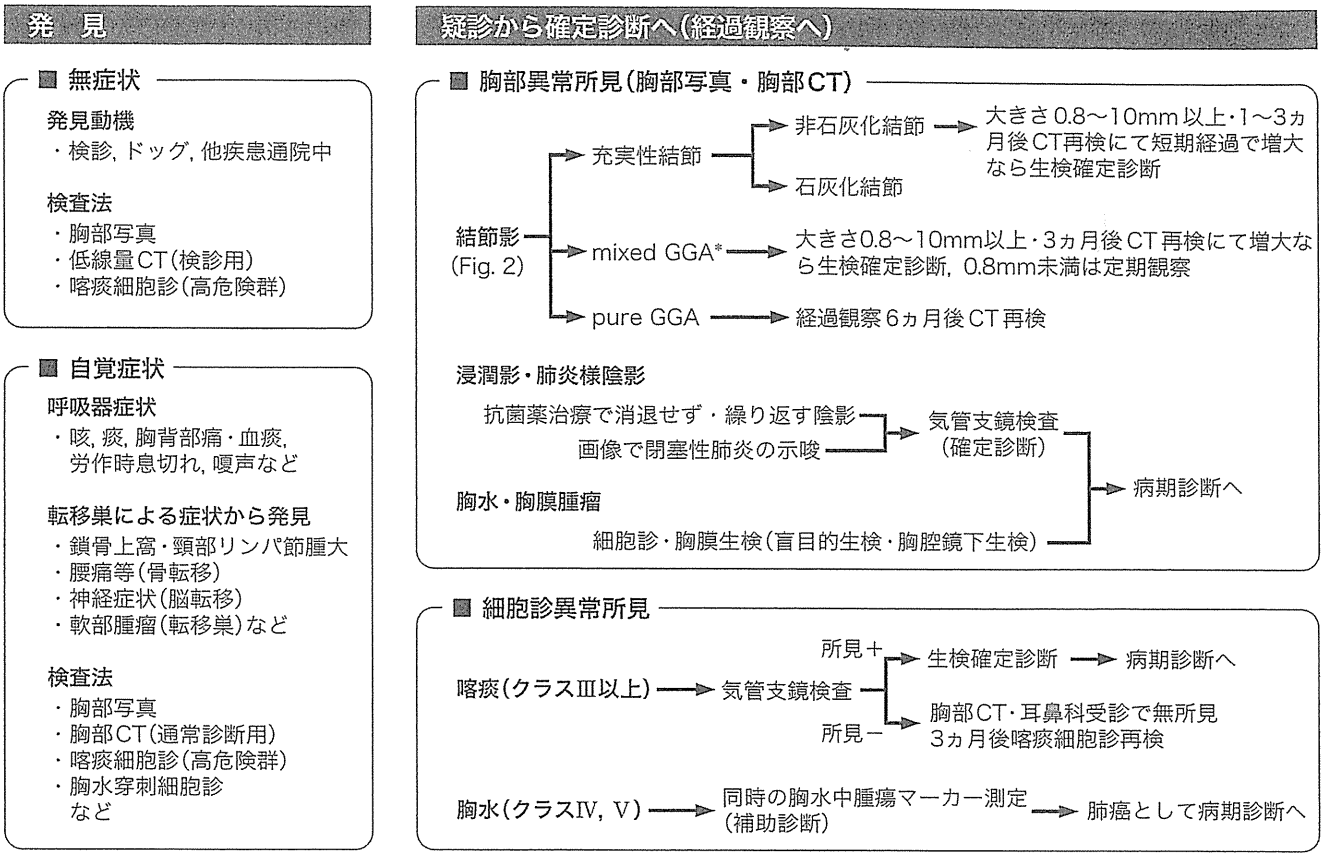

Fig. 1.　肺癌発見～診断までのフローチャート
*GGA：限局性スリガラス陰影．

ることが多い．喀痰細胞診が陽性となりやすく，異常があれば気管支内視鏡検査が必要となる．50歳以上で，重喫煙者（喫煙指数：1日の本数×年数＞600），繰り返す肺炎症状，血痰などは，肺癌の高危険群と考え，胸部写真検査のみならず，3日間の集細胞法による喀痰細胞診を施行する必要がある．末梢肺野に発生する肺野型肺癌に対する喀痰細胞診は，無効である．X線画像で異常陰影を発見することがもっとも重要である．

2．肺癌を疑う症状と血液腫瘍マーカー

肺癌を疑う臨床症状としては，頑固な咳嗽，血痰，胸痛，労作時の息切れ，背部痛など，他の呼吸器疾患にもみられる非特異的なものが多い．増悪する息切れは癌性胸膜炎による胸水貯留，鎖骨上リンパ節腫大をきたす癌腫では，原発性肺癌からの転移がもっとも多い．通常，痛みはあまりなく，非常に堅い腫瘤としてふれる．肺野型肺癌では，脳転移による神経症状，脊椎転移による背部痛で整形外科受診など，遠隔転移による初発症状で他科に受診をする場合も数％にみられる．肺尖部の肺癌（Pancoast腫瘍）の場合は，交感神経浸潤によるHorner症候群や腕神経叢浸潤による上肢の知覚異常を訴えて整形外科や眼科に受診する例がある．頑固な症状，増悪する症状を呈する癌年齢の患者では，喫煙歴を聴取し，肺癌を除外診断する手順が重要である．

血清腫瘍マーカーとしてCEA（carcinoembryonic antigen），SCC（squamous cell carcinoma antigen），CYFRA（cytokeratin 19 fragment），SLX（sialyl stage specific embryonic antigen-1），NSE（neuron specific enolase），pro-GRP（progastrin-releasing peptide）等が一般的に利用されている．代表的なCEAでは，喫煙者の場合に癌がなくともやや高値（10 ng/m*l* ぐらいまで）になることが

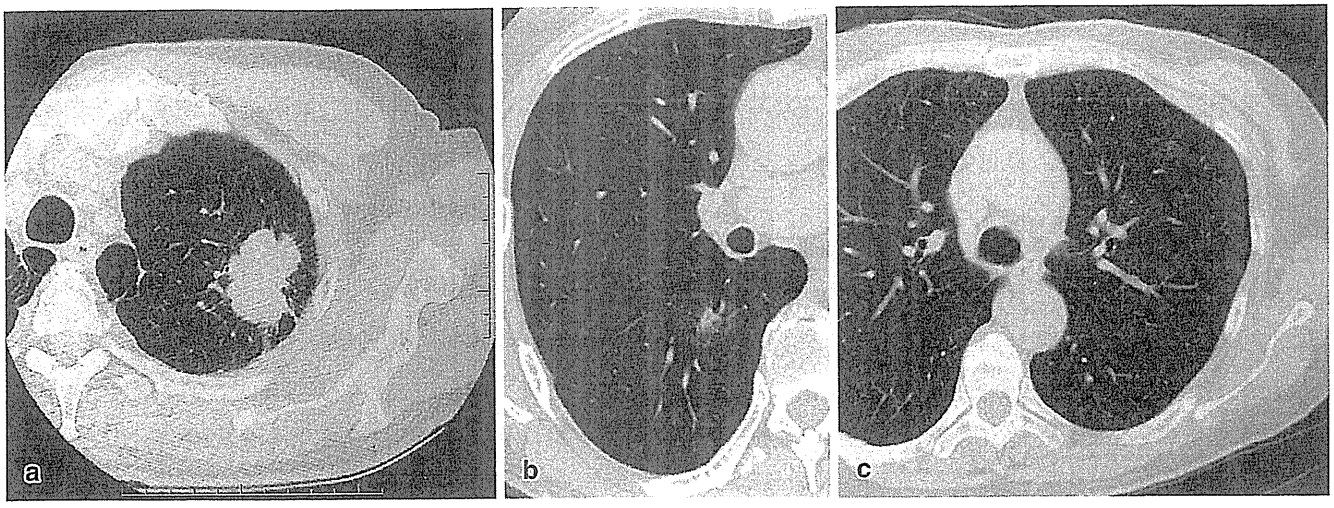

Fig. 2. 結節影の分類(TSCT 画像)
a：充実性結節，b：mixed GGA，c：pure GGA(多発例).

ある．2〜3ヵ月後に再検して上昇傾向ならば精査とする．腺癌系のマーカーとして CA19-9, SLX などがある．慢性気管支炎，気管支拡張症では，CA19-9 が数百 U/m*l* ぐらいの高値を呈することがある．扁平上皮癌系のマーカーとして，CYFRA, SCC があり，小細胞癌では pro-GRP, NSE が特異的である．現在臨床で使用されているこれらの血液腫瘍マーカーは，早期肺癌の診断には役に立たない．治療前に腫瘍マーカーが高値である症例については，治療後の再発モニタリングに有用である．

3．確定診断の重要性

肺門型肺癌を念頭に置いた精査としては，喀痰細胞診陽性や肺炎様陰影で肺門部肺癌を疑うときにはまず気管支鏡検査を行う．可視範囲に所見があれば同部の生検にて確定診断をつける．肺門部肺癌の症例は，第 2，第 3 の多発肺門部肺癌の高危険群なので，完全禁煙をさせて治療後の定期観察が必要となる．肺野型肺癌を疑う異常影を発見したときには，確定診断をつけるために X 線透視下気管支鏡生検，CT ガイド下針生検などを行うが，小型で生検のむずかしい症例などは全身麻酔による胸腔鏡下生検を実施する．進行例では，胸水細胞診やリンパ節針生検細胞診などによる確定診断も行われる．しかし，むずかしい組織型(large cell carcinoma, neuroendocrine type：LCNEC)診断や EGFR(epidermal growth factor receptor)遺伝子変異解析結果などが，肺癌の治療選択に関係することから，細胞診だけでなく，可能な限り組織を採取して確定診断することが要求される．病理組織学的確定診断をつけることは，治療方針を決めるうえで重要であり，また不必要な治療などによる医療過誤を防ぐためにも必要である．

4．腫瘍随伴性症候群

腫瘍随伴性症候群(Table 1)は，がんの直接浸潤や転移による症状ではなく，腫瘍の産生する物質あるいは腫瘍と関係する物質によってがん病巣を離れた部位に生じる臨床症状であり，起因物質としてホルモン類似物質や炎症サイトカインなどの体液性因子などによる作用機序が想定されている．

肥大性肺骨関節症は，膝，肘，手首などの関節痛や，上肢下肢など長管骨に左右対称性に起こる骨痛の症状で発見される．骨皮質に過剰な骨膜反応が起こり，骨 X 線所見での長管骨骨皮質の増成による，骨シンチグラムでの対称的な長管骨への集積が特徴である．骨転移のない症例(とくに肺扁平上皮癌)にみられる高カルシウム血症は，PTH-rP(副甲状腺ホルモン関連蛋白)が関係する．PTH-rP 蛋白は PTH と同様に，骨の吸収作

Table 1. 腫瘍随伴性症候群の例

病態名	原因物質	症　状	肺癌の種類
異所性 ACTH 症候群	ACTH，ACTH 様物質	筋力低下，体重減少，色素沈着，低 K 血症	小細胞癌
ADH 不適合症候群(SIADH)	ADH	倦怠感，精神症状，せん妄，低 Na 血症，血漿浸透圧低下	小細胞癌
高 Ca 血症	PTH-rP	食思不振，嘔吐，腎機能障害，多尿，意識障害	扁平上皮癌
Lambert-Eaton 筋無力症候群(LEMS)	膜電位依存性のカルシウムチャネルに対する自己抗体による神経筋接合部のアセチルコリン放出阻害	近位筋の筋力低下，易疲労感，眼瞼下垂，深部腱反射低下	小細胞癌
肥大性骨関節症	不明	長管骨の疼痛，バチ指	扁平上皮癌
白血球増多症，血小板増多症	コロニー刺激因子(G-CSF，IL-6 など)	発熱，末梢血分画増多	低分化癌，大細胞癌

用があり，カルシウム代謝に作用を及ぼす．高カルシウム血症は，嘔気，全身倦怠感，脱力感，食思不振，心電図異常などがみられ，意識障害，突然の死亡などもある．血中カルシウム濃度測定を行わないと診断はできないことに注意する．治療は，脱水を改善するために十分な補液を行い，ビスホスホネート製剤などを使用する．

肺癌の画像診断

1．CT

約 40 年前に英国で実用化された CT(computed tomography)は，目覚ましい進歩を遂げ，胸部のみならず全身の画像診断法を変革した．10 年前に導入された多列検出器 CT(multi-detector CT：MDCT)は複数列の検出器でデータを同時に収集することで，短時間に広範囲の撮影が可能となり，冠状断像や矢状断像など任意の方向の再構成画像や三次元画像をみることができるようになった．現在では約 5,800 台の MDCT が全国で稼働しており，16 列，64 列 MDCT などが標準的な機種となっている[5]．

胸部単純 X 線では，死角になる肺野部分の結節や，認識されないような淡い濃度の肺野小結節を専門家でなくとも CT により発見できることが利点となっている．撮像データから，より詳細な質的診断・鑑別診断を行うには，0.5～1 mm スライスの thin-section CT(TSCT)再構成画像を利用する．小型結節の辺縁の不整性状，境界の明瞭さ，周囲気管支・血管・胸膜などとの関係，病巣内部の濃度，気腔の残存，スリガラス陰影か充実性結節か(Fig. 2)などを診断のヒントにする．

冠状断像では，腫瘍の気管や気管支との連続性，縦隔側への進展，大血管との関連をとらえやすい．腫瘍と葉間胸膜面との関係の評価は，矢状断像が優れる．MDCT からは大量の情報が生み出され，従来のフィルム画像診断は，MDCT の利点を生かせない．画像モニター診断および診断ワークステーション(画像解析ソフト)が，必須の診断環境となる．また近年，診断支援のための computer-aided diagnosis(CAD)が急速に進歩して[6]，すでに肺野結節の局在診断ソフトを組み込んだ CAD が活用されてきている．

CT で発見される小型肺癌の増加に伴い，確定診断に使用する気管支鏡生検の精度向上が必要となった．MDCT 画像再構成による virtual bronchoscopy(VB)の画像ソフトが開発され，気管支鏡検査中に気管支鏡実画像と VB 画像を対比させながら目標気管支のガイドとするシステムも実用化されている[7]．

本邦には，1 万台以上の CT が稼働しており，医療先進国の中でも CT 機器がもっとも普及している国とされる．近年欧米から，CT 撮影による

国民被曝線量が,他の国々に比較して日本は高く,X線被曝による発癌の増加のリスクが指摘されており,不必要なCT検査を避ける注意が必要である[8]．なお，本邦で検診に用いられている低線量CTは，通常診断用CTに比べて被曝線量が約10分の1に低減されている[9]．

2．MRI

近年のMRI技術の進歩により,肺癌診療におけるMRIの臨床応用は多岐にわたって展開されている．MRIの特性から，肺内空気の存在(低水分含有)や呼吸性移動による画質低下がMRIの短所となり，空間分解能の点ではCT診断能を凌駕するにいたっていない．本邦ではすでに，6,000台以上のMRIが稼動している．MRIの有利な点は，さまざまな撮像法から腫瘤の性状分析ができることであり，脂肪，血液，液体成分などの鑑別が可能となる．体内金属を有する生体に利用できない欠点はあるが，X線被曝のないことが大きな利点となる．

MRIが優位な病態としては腫瘍とそれによる二次性変化(無気肺，閉塞性肺炎)との識別や，頸部腕神経叢(Pancoast腫瘍の場合)，胸壁，心大血管，横隔膜浸潤などの診断がある．造影MR angiography(MRA)が，肺癌の左房浸潤や縦隔，肺門部における血管浸潤の診断能改善に有用であると報告されている[10]．MRIは，種々の撮像法が質的診断に利用されるが，拡散強調画像によるリンパ節診断能向上が指摘されている[11]．遠隔転移診断(M因子診断)としてのMRIが有用である．肺癌に多い病態として脳転移,癌性髄膜炎の画像診断，脊髄転移，脊髄圧迫による横断麻痺，骨転移，筋肉などの軟部組織転移などの質的評価にはMRIがもっとも適している．全身MRI撮像によるM因子検索によって，FDG-PETと同等の評価が可能であることが報告されている[12]．

3．PET

核医学検査としてフルオロデオキシグルコース(2-[fluorine-18]-fluoro-2-deoxy-D-glucose：FDG)を用いたFDG-PET検査は，2002年から肺癌も保険診療の適応疾患となった．本邦では現在600台以上のPETが稼働しており，CTなどの画像診断機器と同じように欧米よりも多い．同時撮像のCT画像との融合画像を診断して，PETの弱点であった空間分解能・形態学的診断能を補うPET-CTが利用されている．糖代謝の亢進した腫瘍細胞に^{18}FをつけたFDGが取り込まれ，FDG-PET画像では強い集積部位として同定される．高血糖状態では，FDGを使用しているので，検査自体が不能となる．肺腫瘤性病変の良悪性の鑑別に有用である．

1,474の肺結節影の診断に関する論文40篇のメタアナリシスでは，感度96.8%，特異度77.8%と報告されている[13]．しかし，PETの空間分解能の限界から，サイズが小さな結節になるとその集積の検出に限界を生じる．とくに，1 cm以下の結節では偽陰性を生じる．肺腺癌へのFDGの集積はグルコーストランスポーターの発現と関連し，発現の少ない高分化腺癌で低く，発現の低分化腺癌で高くなり，分化度とFDG集積が相関することが知られている．

細気管支肺胞上皮癌(bronchiolo alveolar carcinoma：BAC)では糖代謝が低いため，1 cm以上のサイズでも偽陰性になることがある．また，活動性の炎症巣においても集積が認められ，偽陽性が生じることは周知されてきた．投与されたFDGが全身に均等に分布した場合を想定したうえでの相対的な集積程度を示す指標をSUV(standardized uptake value)と呼び，FDG集積の半定量的指標として用いられる．過去にSUVの程度によって良悪性の鑑別を試みる報告がされたが，絶対的な判断基準は得られていない．

病期診断におけるPETの有用性が期待されている．肺癌リンパ節転移診断には，大きさを基準とするCT診断でなく，機能面での診断としてPETによる検索が重視されるようになった．縦隔リンパ節転移の診断精度についてのメタアナリシスによる報告では，非小細胞癌の縦隔リンパ節転移診断の論文でPET 14篇，CT 29篇を解析し，

感度，特異度はPETで79%，91%，CTで60%，77%とPETのほうが診断に優れていた[14]．肺結節診断能に関する44論文のメタアナリシスでは，造影CT，造影MRとPETとでは，感度，特異度等に差を認めなかった[15]．

遠隔転移の診断においてもPETは簡便である．肺癌を対象としてFDG-PETと従来の検査(CT，MRI，骨シンチグラフィー)による病期診断の正診率は，FDG-PETでは83%であったのに対し，従来の検査は65%であった[16]．治療後の経過観察中に腫瘍マーカーが再上昇した場合で病変の場所が特定できないときなどには，PET/CTが威力を発揮する場合がある．なお，PETによるがん検診の有用性は証明されておらず，医療経済学的な視点からも否定的である．

おわりに

新しい肺癌分子マーカーによる血液検査を，早期診断や肺癌高危険群の同定に利用するための研究も行われている．進行癌の状態で発見される肺癌を減らして，肺癌による死亡率低下を狙うには，全国をカバーする肺癌の一次予防・早期発見を目標とする長期的な方策の確立と，禁煙などの市民啓発が必要であり，そのための財源を確保することが急務となっている．また，日常診療での「診断の目」をスキルアップする必要がある．

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肺癌検診は有効か

江口研二

月刊 臨牀と研究 別冊

平成21年7月発行

第86巻 第7号

特集／増加する肺癌―早期診断と治療

肺癌検診は有効か

江口研二

「我が国で行われている胸部写真および喀痰細胞診（重喫煙者のみ）による肺癌検診は，複数の症例対照研究により，肺癌による死亡率減少効果が認められている。大規模無作為化比較試験は行われていないが，公的財源を使う肺癌集団検診の有効性に相応の根拠（エビデンス）はある。」ということが，現状における本稿テーマへの回答である。しかし以下に述べるように，我が国の肺癌検診には，多くの現実的な課題が残されている。

厚労省人口動態統計（2007年）によると，癌による死亡者数は年間33万人にのぼり，肺癌は最も多く年間死亡者数が６万人を越えている。男性肺癌死亡率は，人口10万人対77人で癌死因の第１位である。女性では（人口10万人対27人）大腸癌についで癌死亡率第２位である。喫煙は肺癌の主要なリスク因子であるが，本邦の喫煙率は男性39%，女性11%（2005年）とされ，欧米に比べ依然として高率である。老人健康保健法（老健法）のもとで行われていた肺癌検診では，喫煙指数＝本数/日×年数として600以上の喫煙歴を有する人は，肺門部肺癌（３次気管支分岐までに発生する肺癌）の高危険群とされた[1]。肺門部肺癌は世界的に減少しており，これはフィルタータバコの普及で発癌因子が太い気道より末梢肺に影響を及ぼしているためと説明されている。最近では肺野型肺癌，特に腺癌の症例が過半数を占めている。世界的にも肺野型肺癌の割合が多くなっていて，肺野型肺癌に関する喫煙以外のリスク因子を同定することも急務となっている。肺癌１次予防禁煙対策として，厚労省「健康増進法」施策は，公共の場及び職場での分煙徹底，禁煙支援プログラムの普及，未成年喫煙の廃絶を掲げているが，改善の見通しが立っていない。2007年に策定された国のがん対策推進計画においても，喫煙に関する数値目標は削除されてしまった。欧米では，すでに肺癌による死亡率は明らかな減少傾向にあり，これは20年以上前から実施されてきた禁煙キャンペーンの効果と説明されている。近年，日本の肺癌年齢調整死亡率は頭打ち傾向にあるが，再度上昇傾向も認められ，また高齢者の増加とともに肺癌の患者数は増加している。診断時点で約６～７割の患者が既に進行癌であり，治り得る時期の肺癌を数多く見つけることは緊急の課題である。治癒できる肺癌の大きさはどのくらいまでか？　切除成績から判断すると本邦の日本肺癌学会，日本呼吸器外科学会，日本呼吸器学会が合同で組織している肺癌登録合同委員会による大規模調査では臨床病期Ⅰａ期の５年生存率は80%をこえる。原発巣の大きさを１cm以下に限ると切除例のリンパ節転移頻度は数%以内であり，転移のない例の５年生存率は90%以上となっている。また，Ⅰ期肺癌の中でも１cm以下，１～２cmと原発巣の大きさを区切って比較した成績では，小さいものの治療成績が明らかに良い。従って直径１cm内外の肺癌を目標とすることが，治りうる患者を早期に見つけるという検診の目安といえる。

Ⅰ．肺癌検診の体制と有効性の指標

検診は，禁煙のように癌の原因を絶つのではなく（１次予防），癌になったものを早期に発見する２次予防である。集団検診の目的は，公共資金により，ある時期にできるだけ多くの対象者を検診することで，当該疾病による死亡者数の減少を実現することである。日本で普及している人間ドックは，希望者が自己資金を使って検査を受けるものである。前者を対策型検診（organized screening），後者を任意型検診（opportunistic screening）といって区別している。対策型検診実施の前提は，その検診によって肺癌死亡率減少効果が見られることである。検診方法論が妥当で

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