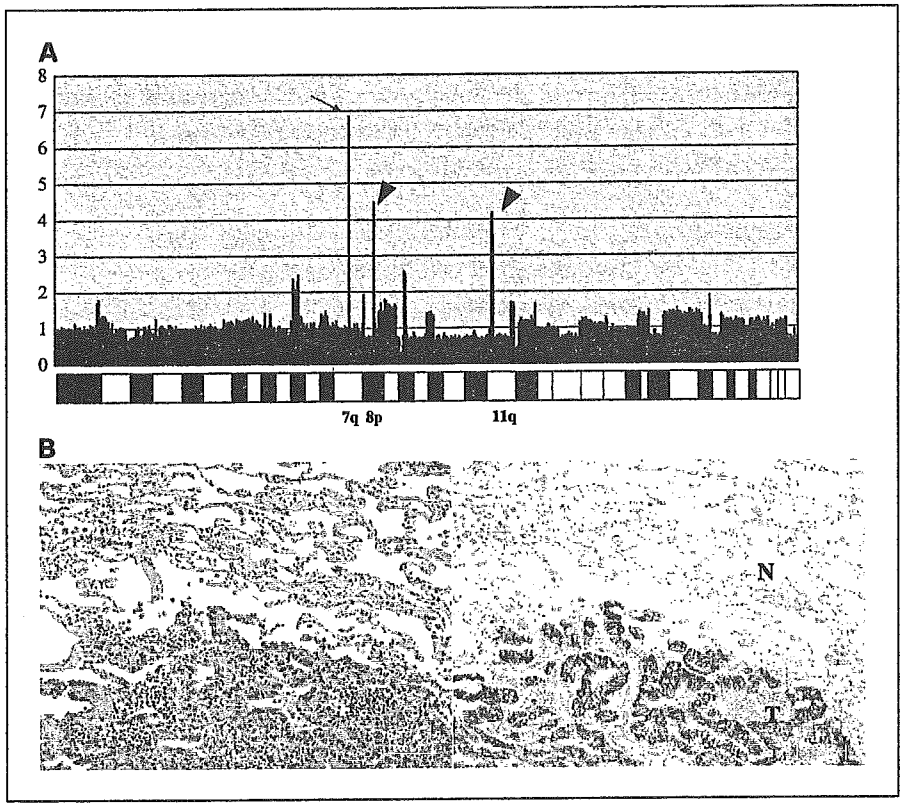

Fig. 3. Amplification and overexpression of MET in lung adenocarcinoma. *A*, a chromosomal copy number alteration profile of a lung adenocarcinoma with an amplification of *MET* locus. Each signal ratio (tumor/normal) of 800 examined loci was plotted from chromosome 1p (*left*) to Y (*right*). Each chromosome is represented by underlining boxes as in Fig. 1A. Chromosomal arms (7q, 8p, and 11q) with high-level amplifications were indicated. More than 6-fold amplification of a bacterial artificial chromosome containing the *MET* gene (*7q21*) was detected (*arrow*). This tumor also showed amplifications on 8p and 11q (*arrowheads*). *B*, immunohistochemical analysis of MET protein expression in the same case (×200). Four-micrometer sections of formalin-fixed, paraffin-embedded specimens were stained with H&E (*left*) and an anti-MET monoclonal antibody (*right*). Overexpression of the MET protein in tumor cells (*T*) was observed compared with the surrounding noncancerous lung tissue (*N*). All MET-amplified tumors exhibited prominent membranous and cytoplasmic expression. *Bar*, 200 μm.

55 cases and 36.3% of total cases, respectively) shared many genetic alterations but also had changes unique to each other. This implied that they may be derived from a common precursor and diverge via the acquisition of specific genetic alterations during tumor development. In contrast, the third subclass (cluster B, 15 of 55 cases, 27.3%) showed characteristically fewer genetic alterations than the other two. Although one would expect this group to consist of tumors of an earlier stage, it contained tumors that varied clinically (from stage I to stage III) and there was no significant correlation of histopathologic features with the above classification. Interestingly, this clustering classification is significantly associated with smoking habits, suggesting that the specific carcinogen exposure may affect overall genetic profile of lung cancer. We propose three possibilities for the carcinogenesis process in the third group; these tumors may predominantly acquire (*a*) genetic alterations not covered by our arrays, although they contain most of the known cancer-related genes; (*b*) genetic alterations that do not involve copy number changes, such as balanced chromosomal translocations or microsatellite instability (37, 38); or (*c*) epigenetic alterations such as aberrant methylation of gene promoters, which have been reported to associate with smoking history (39). Further analysis of this group, focusing on the above mechanisms, will provide a more complete view of lung carcinogenesis.

Because the *EGFR* gene is frequently altered in lung adenocarcinoma and its mutation status is correlated to the sensitivity to the specific inhibitor, Gefitinib (8–10), we assumed that the *EGFR* pathway plays important roles in lung cancer and examined whether *EGFR* mutated tumors have any genetic characteristics in nature. We detected the *EGFR* gene mutations at similar frequency as reported (31, 32, 40) and the presence of somatic mutations was significantly associated with never-smoking history as previous studies reported (8–10, 31, 32, 40). We detected K-*ras* mutations relatively less frequent than previously reported (41) but comparatively to other study (42) probably because our analyzed cases contained more female and nonsmokers. We found that *EGFR* mutation and K-*ras* mutation were mutually exclusive as reported (31, 32, 40) and this finding is consistent with the notion that activation of both *EGFR* and K-*ras* stimulates the same downstream pathway (43).

We identified 58 loci whose alterations significantly correlated with the presence of *EGFR* mutations. It is interesting to note that amplification of the *EGFR* gene itself is significantly observed in *EGFR* mutated tumors, indicating that both somatic mutation and amplification of the *EGFR* gene simultaneously occur in part of lung adenocarcinoma. Using these selected loci, we classified the tumors by supervised hierarchical clustering. This classification revealed two groups: one containing only *EGFR* wild-type tumors (EGFR-WT) and the other (EGFR-MUT) containing all *EGFR* mutated and some *EGFR* wild-type tumors. Because the *EGFR* wild-type tumors that were grouped with the EGFR-MUT group shared similar genetic alterations with the *EGFR* mutated tumors, we hypothesized that they may have unknown genetic alterations complementary to *EGFR* activation and subsequently examined loci containing oncogenic receptor–type tyrosine kinases in our arrays. We found that a locus (*7q21*) containing the *MET* gene was amplified in part of these *EGFR* wild-type tumors and immunohistochemically validated overexpression of MET protein in these tumors. MET was shown to be implicated in *ras*-mediated tumorigenicity (44, 45) and activated in many tumors (34–36). Although the number of cases with MET amplification is small in this study, it is tempting to speculate that amplification of the *MET* gene may play a role similar to *EGFR* mutation in lung adenocarcinoma. Recently, somatic alterations of the *MET* gene were detected in lung cancer and pharmacologic inhibitors specific to the MET kinase have been

reported (46–48). Our results also support the idea that the MET oncoprotein is a potent new candidate for therapeutic target in lung adenocarcinoma although there was no somatic mutation in the analyzed exons of our cases. In our cases, there are seven tumors without either *EGFR* mutations or *MET* amplification in the EGFR-MUT group. Somatic mutations in the kinase domain of *ERBB2* were reported in *EGFR* wild-type lung adenocarcinomas (7, 33). Therefore, we searched for *ERBB2* mutations in all 55 cases and found no somatic mutations, suggesting that other oncogenic kinases might be involved in these tumors.

EGFR mutation status could not predict tumor recurrence, which is consistent with a previous report on the insignificant relationship between *EGFR* mutation and patient prognosis (40). However, we found that EGFR-MUT group, which is revealed by genetic classification, showed significantly shorter disease-free survival than EGFR-WT group. Our results imply the possibility that specific combinations of genetic alterations (genetic code) selected by genome-wide analysis could evaluate tumor characteristics and estimation of such codes would be applicable for diagnostic purposes. Our classification also revealed that there are two genetically distinctive subgroups in the *EGFR* mutated lung adenocarcinoma, which were associated with tumor histologic differentiation. Because Gefitinib is one of the most promising molecular target drugs against lung cancer and molecular mechanisms determining its efficacy are still unclear (49), further analysis of a larger cohort is warranted to determine any possible relationship of genetic profiling with sensitivity to chemotherapeutic agents, including tyrosine kinase inhibitors.

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Institutional report - Thoracic general

The new strategy of selective nodal dissection for lung cancer based on segment-specific patterns of nodal spread☆

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Abstract

A new strategy for selective nodal dissection in non-small cell lung cancer (NSCLC) patients according to the segment of primary tumor was explored. Data on 504 patients with NSCLC of less than 5 cm, histologically revealed to be N2 disease after thoracotomy, were analyzed. In right upper lobe (RUL) tumor, when the pretracheal node was negative, the incidence of subcarinal involvement was 3.8%. In lower lobe tumor, superior segment (RLL-Superior and LLL-Superior) tumor showed a significantly higher incidence of superior mediastinal involvement than basal segment (RLL-Basal and LLL-Basal) tumor (right, $P=0.0036$; left, $P=0.0499$). When the subcarinal node was negative, the incidence of superior mediastinal metastasis in RLL-basal and LLL-Basal tumor was 11% and 8%, respectively. In left upper lobe tumor, superior segment (LUL-Superior) tumor showed a significantly lower incidence of subcarinal involvement than lingular segment (LUL-Lingular) tumor ($P=0.0381$). When aortic nodes were negative in LUL-Superior tumor, the incidence of subcarinal metastasis was 6%. Collectively, in RUL and LUL-Superior tumors, subcarinal dissection may be unnecessary if superior mediastinal node is negative. In RLL-Superior and LLL-Superior tumors, extensive dissection is required. In RLL-Basal and LLL-Basal tumors, superior mediastinal dissection may be unnecessary if subcarinal node is negative.

Keywords: Selective nodal dissection; N2; Systematic nodal dissection; Non-small cell lung cancer

1. Introduction

Since Cahan (1960) [1] reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, which was called radical lobectomy, this procedure has been a standard surgery for lung cancer. In 1978, Naruke [2] suggested an anatomical map in which the lymph node stations were numbered, and since then this map has been used for nodal dissection. With this map, extensive nodal dissection including the superior and inferior mediastinum has been universally performed in lung cancer surgery. This technique, termed systematic nodal dissection (SND) remains an important component of the investigative and therapeutic process in all patients undergoing thoracotomy for lung cancer.

However, as the number of early-detected lung cancers is increasing with the recent development of the CT scanner, the extent of nodal dissection for lung cancer should be tailored to each case. That is, more selective dissection should be undertaken especially for early cancer by considering the tumor location-specific lymphatic pathway, simply because nodal involvement is not so extensive in many cases. In this study, a new strategy for selective nodal dissection in non-small cell lung cancer (NSCLC) patients based on segment-specific patterns of nodal spread was explored.

2. Materials and methods

2.1. Patients

Data on 504 patients with NSCLC less than 5 cm, histologically revealed to be N2 disease between January 1977 and October 2003, were analyzed. Tumors invading the other lobe were excluded. All patients underwent at least lobectomy with hilar and mediastinal lymphadenectomy. The correlation between the segment of the tumor location and the involved hilar/mediastinal nodes were investigated in each case.

2.2. Surgical procedure

Pulmonary resection and SND were performed through posterolateral thoracotomy. At thoracotomy the diagnosis was confirmed by frozen-section analysis, if histological confirmation was not available preoperatively. Systematic nodal dissection, including the superior to inferior mediastinum, was then performed after pulmonary resection. In left thoracotomy, upper mediastinal dissection indicated aortic (#5, 6) and tracheobronchial (#4) node dissection.

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Table 1
Patient characteristics in pathological N2 non-small cell lung cancer patients less than 5 cm in size

Number of patients	504
Histological type	
Adenocarcinoma	367 (72.8%)
Squamous cell carcinoma	99 (19.6%)
Large cell carcinoma	27 (5.4%)
Adenosquamous carcinoma	9 (1.8%)
Others	2 (0.4%)
Tumor location	
Right	303
upper lobe	183
middle lobe	25
lower lobe	95
Left	201
upper lobe	140
lower lobe	61

2.3. Patient characteristics

Patient characteristics are shown in Table 1. The tumor cell types were adenocarcinoma in 367 (72.8%), squamous cell carcinoma in 99 (19.6%), large cell carcinoma in 27 (5.4%) and adenosquamous cell carcinoma in 9 (1.8%). Right thoracotomy was performed in 303 patients and left in 201. The lobe of origin was the right upper lobe (RUL) in 183 patients, right middle lobe (RML) in 25, right lower lobe (RLL) in 95 in 41 of whom it was the superior segment, left upper lobe (LUL) in 140 in 122 of whom it was the superior segment, and left lower lobe (LLL) in 61 in 23 of whom it was the superior segment.

2.4. Statistical analysis

The statistical significance of differences was determined using the chi-square test for independence. Relative risk and 95% confidence intervals were calculated. Values of P less than 0.05 were considered to be statistically significant.

3. Results

3.1. RUL tumor

The incidence of subcarinal involvement in RUL tumor was 18% (33/183). However, when the pretracheal lymph node (#3) was negative, the incidence was only 3.8% (7/183). There were no significant differences in patterns of lymphatic pathway between the apical, posterior and anterior segments within the RUL.

Table 2
The incidence of upper mediastinal metastasis in superior and basal segment tumor of the lower lobe

Side	Location of the primary tumor	No. of patients	Metastasis to the superior mediastinal nodes		
			No.	%	P value
Right	Superior segment	41	26	63	0.0036
	Basal segment	54	18	33*	
Left	Superior segment	23	15	65	0.0499
	Basal segment	38	15	39**	

* When subcarinal lymph node (#7) was negative, the incidence of superior mediastinal (#1–4) metastasis was 9% (5/54).
** When subcarinal lymph node (#7) was negative, the incidence of superior mediastinal (#4, 5, 6) metastasis was 8% (3/38).

3.2. RML tumor

The incidence of superior mediastinal (#1–4) and subcarinal (#7) involvement was 52% (13/25) and 72% (16/25), respectively. The incidence of lower mediastinal involvement was 8% (2/25). There were no significant differences in patterns of lymphatic pathway between lateral and medial segment within the RML.

3.3. RLL and LLL tumor

Among all of the segments in the lower lobe, 5 segments in the right lung and 4 in the left, there were significant differences in patterns of lymphatic pathway between the superior and basal segments on both sides, as shown in Table 2. The incidence of superior mediastinal involvement in superior segment tumor (right 65%, 26/41; left 65%, 15/23) was higher than that in basal segment tumor (right 33%, 18/54; left 39%, 15/38), with significant differences (right, $P=0.0036$; left, $P=0.0499$). When the subcarinal lymph node (#7) was negative, the incidence of superior mediastinal metastasis in RLL-basal and LLL-Basal segment tumor was 9% (5/54) and 8% (3/38), respectively.

3.4. LUL tumor

There were significant differences in patterns of lymphatic pathway between the superior and lingular segments within the LUL, as shown in Table 3. Superior segment tumor showed a significantly lower incidence of subcarinal involvement (14%, 17/122) than lingular segment tumor (33%, 6/18) ($P=0.0381$). When aortic lymph nodes (#5, 6) were negative in superior segment tumor, the incidence of subcarinal metastasis was 6% (7/122).

Collectively, the following eight segments, four in each side lung, with specific lymphatic pathways were identified: RUL ($n=183$), RML ($n=25$), superior segment of the RLL (RLL-Superior, $n=41$), basal segment of the RLL (RLL-Basal, $n=54$), superior segment of the LUL (LUL-Superior, $n=122$), lingular segment of the LUL (LUL-Lingular, $n=18$), superior segment of the LLL (LLL-Superior, $n=23$) and basal segment of the LLL (LLL-Basal, $n=38$). Based on the abovementioned patterns of nodal spread, the proper strategy for the selective lymph node dissection of each segment is shown in Table 4.

4. Discussion

The pathological nodal status in lung cancer patients is not always the same as that predicted by pre-operative investigations. For TNM classification, CT scan has been used in the clinical diagnosis of nodal status, however, the sensitivity of CT scan for the N factor is reported about 64 to 77% [3]. Since a high incidence of false-negative nodes on CT scan has been reported [4], systematic nodal dissection (SND), which means extensive mediastinal dissection including superior to inferior mediastinum, has been per-

Table 3
The incidence of superior mediastinal and subcarinal metastasis in superior and lingular segment tumor of the left upper lobe

Location of the primary tumor in the left upper lobe	No. of patients	Metastasis to the superior mediastinal nodes (#4,5,6)			Metastasis to the subcarinal node (#7)		
		No.	%	*P* value	No.	%	*P* value
Superior segment	122	118	97	NS	17	14*	0.0381
Lingular segment	18	13	72		6	33	

* When aortic nodes (#5, 6) were negative, the incidence of subcarinal metastasis was 6% (7/122).

formed for lung cancer patients undergoing thoracotomy. Pathological evaluation of nodal involvement at the mediastinal and hilar levels is essential for detailed assessment of the disease extent.

Graham and associates [5] suggested that SND could disclose unexpected N2 disease, irrespective of cell type, the size, location and lobe of origin of the primary tumor, and whether prior mediastinoscopy had been performed. Keller and associates [6] suggested that cure rates could be improved by SND. Therefore, SND has been accepted as an important component of the investigative and therapeutic process in NSCLC patients.

With the development of the CT scanner and the increased incidence of lung cancer, the number of early-stage lung cancer is rising. The incidence of small-sized lung cancer among resected primary lung cancers in recent years has exceeded 20% in Japan [4,7]. As the number of early-detected lung cancers is increasing, a new therapeutic strategy for nodal dissection is required. Proposals of limited surgery for lung cancer have been undertaken in some previous reports [8–10].

There are two methods of limited surgery, one is lung parenchyma-preserving surgery and the other is limited nodal dissection. Regarding the lung parenchyma-preserving surgery, Lung Cancer Study Group (LCSG) [11] reported the results of a randomized trial of lobectomy versus limited resection for T1N0 NSCLC. They observed a 75% increase in recurrence and a 50% increase in cancer death in the patients undergoing segmentectomy or wedge resection, compared to those in the patients who underwent lobectomy. It is difficult to select candidate patients for limited resection, because cT1N0 lung cancer patients show nodal disease with a 15 to 25% incidence [4,7].

As for limited lymph node dissection, Riquet and associates [12] reported that lung cancer metastasizes so easily to the mediastinum that selection of the patients for limited surgery should be discussed carefully. Some previous reports have described the appropriateness of selective nodal dissection based on the lobe-specific extent of nodal spread [13–15]. In this study, we evaluated more meticulous data of the lymphatic pathway in not only T1 but also T2 tumors, to collect as much data as possible, and proposed a method of limited dissection from these results as shown in Table 4. The strategy of lymph node dissection should be changed from extensive dissection to selective dissection especially in early stage cancer or poor risk patients, because selective dissection will be able to reduce postoperative morbidity, such as bronchopleural fistula, chylothorax or recurrent nerve palsy. The establishment of a universally accepted method of selective nodal dissection for lung cancer would be indispensable.

5. Conclusions

Based on the patterns of nodal spread, a proper strategy for selective lymph node dissection of each segment was proposed as shown in Table 4. In RUL and LUL-Superior tumors, subcarinal dissection may be unnecessary if the superior mediastinal node is negative on frozen section. In RML and LUL-Lingular tumors, superior mediastinal and subcarinal dissection is necessary. In RLL-Superior and LLL-Superior tumors, extensive systematic dissection is routinely required. In RLL-Basal and LLL-Basal tumors, superior mediastinal dissection may be unnecessary if the subcarinal node is negative on frozen section.

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Table 4
The strategy of selective nodal dissection based on segment-specific patterns of nodal spread

	Location of the main tumor			
	RUL LUL-Superior	RML LUL-Lingular	RLL-Superior LLL-Superior	RLL-Basal LLL-Basal
Superior mediastinal nodes *3	⊙	⊙	⊙	O*2
Inferior mediastinal nodes				
Subcarinal node (#7)	O*1	⊙	⊙	⊙
Paraesophageal (#8) and pulmonary ligament (#9) nodes	×	×	⊙	⊙

⊙ dissection is advisable, O dissection is not always necessary, × dissection will be unnecessary.
*1: dissection may be unnecessary if pretracheal node (#3) is negative on frozen section.
*2: dissection may be unnecessary if subcarinal node (#7) is negative on frozen section.
*3: #1–4 for the right side, and #4–6 for the left.

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Appendix. Conference discussion

Dr. P. van Schil *(Edegem, Belgium)*: I think this is especially important as within the ESTS we are working on guidelines for peroperative mediastinal staging.

I have two questions for you. Did you observe any difference with the previous studies performed by Japanaese surgeons; for example, the classical studies by Naruke? Secondly, you state that you do segment-specific nodal dissection. On the other hand, you consider the upper lobe and the middle lobe just as 1 segment, but, in fact, anatomically there are 3 segments in the upper lobe and 2 in the middle lobe, or doesn't it matter for those 2 lobes?

Dr. Watanabe: Let me anaswer the second question first. I checked all of the segments in the right upper lobe and middle lobe, that is, the apical, posterior and anterior segment in the upper lobe, and the lateral and medial segment in the middle lobe. But there are no specific pathways among those segments, so I divided just the right upper lobe and the right middle lobe.

I'm sorry, what was the first question?

Dr. van Schil: Did you observe any differences with previous studies performed by the Japanese surgeos; for example, the studies by Naruke?

Dr. Watanabe: Unfortunately, no.

Dr. D. Branscheid *(Grosshandsdorff, Germany)*: Do you think that there are sometimes reasons why the lymph nodes are flowing more in a certain direction and all of a sudden there are 2 or 3 and the flow is to another side? Did you check if they have had tuberculosis or other infections? Have those lymph nodes been enlarged or have they been normal on the CR scan? Can you give us something about that?

Dr. Watanabe: I didn't check all of your suggestions. We basicaly do surgery only for clinical N0 and N1 patients.

Dr. Branscheid: Let me just ask another question. When the situation is like that, isn't it just an argument to do a complete dissectin and not say, okay, this node is not involved, therefore I probably do not need to take the next one? This is the consequence that I take out of your presentation. Is that wrong, or do you see it like that also a little bit?

Dr. Watanabe: Your question is why we are exploring the selective nodal dissection, why we don't do systematic nodal dissection?

Dr. Branscheid: No. Is the consequence to do a complete dissection? Is this your consequence out of that?

Dr. Watanabe: No. Recently, with the development of the CT scanner in Japan, we are getting a large number of early lung cancers. Basically we need to do systematic nodal dissection for lung cancer patients, but for early stage lung cancer we don't think systematic dissection is required for all of the tumors. This is the reason why we started this study. But the candidate in this study was the patients who underwent systematic dissection. So basically we think that systematic dissection is very important for lung cancer.

Dr. S. Elia *(Rome, Italy)*: You said that in 8 of 12 cases, actually in 66%, you would advice lymph node dissection. So you leave only 33% of lymph nodes that are actually doubtful. Would you feel safe in not performing complete lymphadenectomy in these patients? What is your conclusion?

Dr. Watanabe: I just took only pathological N2 patients. But among all patients, I mean N0, N1 and N2, if we included those patients, the incidence is going down, and I think the incidence will be one-third of this figure. So I think if the incidence is less thatn 10%, the incidence among all the lung cancer patients will be a few percent.

Dr. A. Turna *(Istanbul, Turkey)*: Could you tell us how many of your patients had mediastinoscopy before resection? Did you perform mediastinoscopy in these patients?

Dr. Watanabe: Very few: Basically we do mediastinoscopy for clinical N2 patients, and they are actually N2 on the mediastinoscopy. So we excluded those patients. In this study, the number of patients who underwent mediastinoscopy is very few.

Dr. B. Passlick *(Freiburg, Germany)*: What is your strategy for the future? Will you leave the upper mediastinal nodes in place if you have a right lower lobe tumor and a negative forzen section on the No. 7 lymph nodes?

Dr. Watanabe: We are now studying that kind of selective dissection. If the hilar lymph node and the No. 7 lymph node are negative in basal segment tumor, we can omit the upper mediastinal dissection. But now we are conducting only for poor-risk patients or very early lung cancer patients.

Meeting Summary of the 12th International Conference on Screening for Lung Cancer: Nara, Japan, April 2005

Kenji Eguchi, MD, PhD, and Claudia Henschke, MD, PhD†*

(*J Thorac Oncol.* 2006;1: 190–197)

The 12th International Conference on Screening for Lung Cancer, hosted by the Screening Committee of the Japan Lung Cancer Society, was held in Nara, Japan on April 8–10, 2005. The International Early Lung Cancer Action Program (I-ELCAP) has conducted regular conferences semiannually both at Weil Cornell Medical College in New York, NY and at other I-ELCAP sites in the world. This 12th conference was a landmark of I-ELCAP activity for 6 years. Low-dose computed tomographic (LD-CT) scan was experimentally introduced for lung cancer screening in both Japan and the United States in 1993. Commemorating the pioneering work on LD-CT screening for lung cancer for a decade by both the ELCAP and the Japanese group, this I-ELCAP conference was hosted by the Screening Committee of the Japan Lung Cancer Society under the auspices of the Japan Lung Cancer Society, the Japanese Respiratory Society, the Japanese Society for Respiratory Surgery, the American Cancer Society, and the International Association for Studies of Lung Cancer (IASLC). The broadest mission of these conferences is the collective pursuit of avant-garde understanding of the issues surrounding screening for lung cancer, the broadest subissues being early diagnosis and early intervention. Any given conference focuses on issues that are of particular interest at the time. As always, the conference provides an update of research on and practice of screening for lung cancer, including updates of I-ELCAP protocols and results of research. For the conference, more than 180 attendees from eight countries, including non-members of the I-ELCAP, gathered in Nara, one of the ancient capitals of Japan in the seventh to eighth century (Figure 1).

The 10th and 11th Conferences focused on the results on the diagnostic performance of the I-ELCAP protocol for CT screening and on alternatives to resection in early intervention. These conferences also focused on the discussion between individuals seeking screening and their physicians such as the potential benefit of a single round of screening. However, it requires the likelihood that early intervention could cure such a cancer, and that the patient would avoid death from another cause for a decade or another specified period. The 12th International Conference aimed to summarize the evaluation by I-ELCAP and Japanese groups as to the benefit of CT screening for lung cancer.

CONSENSUS STATEMENT

This Nara conference addressed the two broad missions of these conferences: advancement policy (relevant research on early diagnosis of lung cancer) and translation of up-to-date findings into guidelines for practice based on the accumulated evidence from the I-ELCAP consortium. Experiences with screening performed by individual institutions were presented for the Japan Association against Lung Cancer (ALCA), Hitachi's employee screening program, and the Mayo Clinic screening program. The Japanese Lung Cancer Screening Study (JLCSS) group reported on its nationally based study comparing 46,733 people who had at least one CT screening test with 91,970 people who had at least one chest radiographic screening. I-ELCAP presented its data for more than 28,000 people who have had more than 50,000 screenings. Thus, this conference reviewed the largest studies ever conducted with CT screening for lung cancer.

The final results of the JLCSS will be reported in 2007, but a 2005 interim report indicated that it will show a reduction in deaths from lung cancer as a result of screening. The I-ELCAP presented its approach to screening research, development of the regimen and assessing its benefit, and distinguishing between the screening's diagnostic and prognostic implications. Diagnostically, the concern centers on how early the diagnosis of lung cancer can be achieved while minimizing work-up, including biopsies. Relative to prognosis, the issue is the preventability of death from lung cancer by early intervention based on early diagnosis. In the I-ELCAP experience, more than 80% of diagnoses have been achieved at stage I, with 90% of the biopsies resulting in a diagnosis of malignancy. Critical in the regimen is the identification of growth consistent with malignancy. The I-ELCAP also presented results pertaining to prognosis. These confirm that screen-diagnosed lung cancers presenting as solid nodules lead to death if not treated, whereas some cases of adenocarcinoma presenting as a non-solid nodule may be so slow-growing as to be unlikely to be fatal for a short time if not treated. It is estimated that more than 80% of deaths from lung cancer could be prevented by early intervention under CT screening. The I-ELCAP also discussed competing

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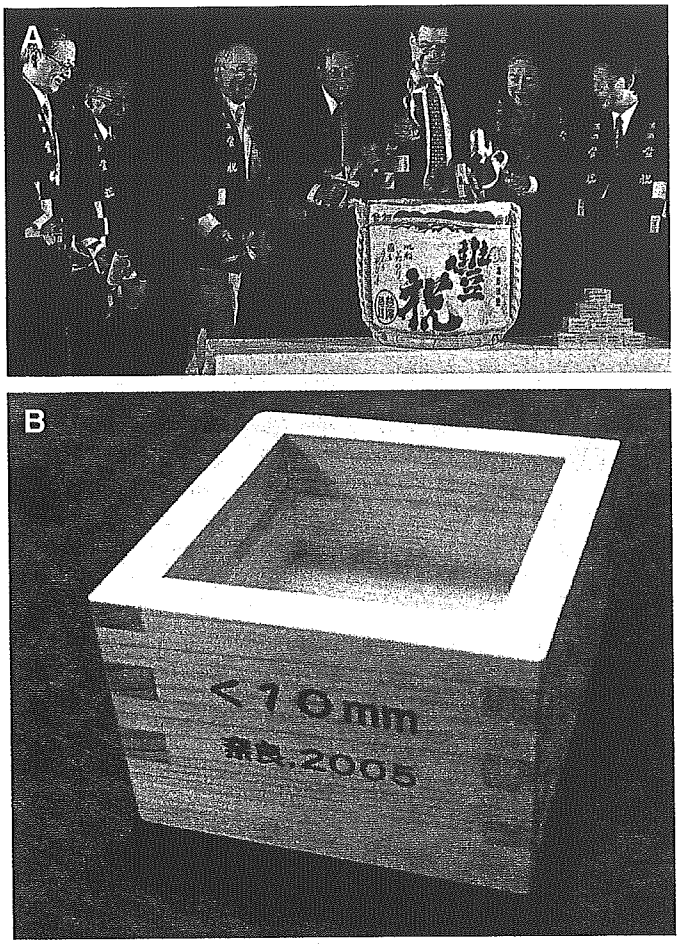

FIGURE 1. (A) "Kagamibiraki," Opening a Japanese sake barrel head at the reception (the Garden of Nara-Ken New Public Hall). (B) A wooden cup for Japanese sake printing <10 mm. It is challenging to detect nodules <10 mm in diameter, that is, "curable lung cancer."

causes of death in the highest-risk subcohort of people aged 60 to 75 years with at least 30 to 80 pack-years of smoking. It found that the 5- and 10-year rates of death from causes other than lung cancer (conditional on not dying from lung cancer) were low, 3% and 7%, respectively.

I-ELCAP surgical and radiotherapy results were presented together with those of Japanese studies on limited resection, transbronchoscopic brachytherapy, percutaneous microwave and radiofrequency ablation, cryosurgery, heavy-particle radiation therapy, and stereotactic radiation therapy. Pathologic and molecular features of early cancer were also presented. These results provided the foundation of new treatment trials on screen-diagnosed lung cancers.

Three workshops were held. One of these focused on the methodological advances and safety of CT-guided fine-needle aspiration biopsy and issues of follow-up in biopsy-negative cases central to a regimen of screening. Another workshop focused on multicenter treatment trials, such as different protocols depending on CT features of nodules and the critical issues to be studied. The third workshop focused on computer-aided detection and characterization to deal with the increasing number of images per person that can now be produced by a single CT scan.

ORAL PRESENTATIONS: CURRENT STATUS AND EXPLORATORY STUDIES OF LUNG CANCER SCREENING

Keiichi Nagao, MD, (Safety and Health Organization, Chiba University, Japan) discussed practical problems in the application of LD-CT screening in Japan. In Japan, more than 100,000 subjects received LD-CT scans as practice-based opportunistic screening annually. These screenings are partly supported by local governments or by insurance in Japan. He addressed five major issues: reducing cost to the individual for screening, increasing subsidies from local governments, expanding the training of specialists for LD-CT reading, application of computer-aided diagnosis (CAD), and qualification of hospitals that had specialists to perform further examinations and treatment for small lung cancers detected in screening.

Tomotaka Sobue, MD, (Research Center for Cancer Prevention and Screening, National Cancer Center Tokyo) presented the historical background of lung cancer screening in Japan. The lung cancer screening system has been developed based on well-established mass screening system for tuberculosis, which had been in operation since 1951 and continued in the 1970s and 1980s. In 1987, lung cancer screening using chest radiographs (and sputum cytology for high-risk populations) for people aged 40 years or older was introduced as a national policy under the Health Services Law for Aged. This decision was not based on direct evidence of a benefit from lung cancer screening in terms of a reduction of mortality. Since 1992, six case-controlled studies from different large groups of Japanese have been published. Although they were retrospectively analyzed, all studies indicated beneficial effects, and four studies showed statistically significant mortality reductions of lung cancer. There is no evidence that the difference between the trend of incidence and mortality of lung cancer has been widened in Japan, and the facts indicate that lung cancer screening in Japan has not been effective at a national level. However, in the areas in which these studies were conducted, lung cancer mortality among women aged 50 to 74 years has been decreasing. Lung cancer screening using chest radiographs and sputum cytology is effective only when it is applied with high quality assurance, and many of the systems in Japan have not reached this level.

Hironobu Ohmatsu, MD, (National Cancer Center East Hospital, Japan) presented the 10 year-experience of LD-CT screening in the ALCA project in Tokyo. ALCA is a for-profit organization to screen dues-paying members (smokers aged 40 years or older) for lung cancer that was established in 1975 by Shigeto Ikeda, MD, who had was the first to develop flexible bronchofiberscopy. In 1993, LD-CT was introduced as a screening device at ALCA. Multi-detector CT (four rows) has been used since 2002. Using 15 mAs of radiation exposure, the data were acquired with 2-mm collimation and 10-mm reconstruction. From 1993 to 2004, a total of 18,331

screenings have been performed, and 76 lung cancers (0.44%) have been detected. Compared with historical data, the ALCA detection rate was 3 times higher than that of screening with a chest radiograph. Ninety two percent of the cancers were peripheral type, and 62% were adenocarcinoma. Mean tumor size was 17 mm, and 80% were stage I (74% stage IA). The 5-year survival rate was 80.4%. In terms of stage shift in patients with invasive adenocarcinoma, results showed statistically significant shifts to early stage (stage I) among the detected lung cancers during long-term repeated LD-CT screening for more than 10 years. In other histology, no statistically significant stage shift was seen.

James Jett, MD, (Mayo Clinic, USA) summarized the final results of the Mayo trial on LD-CT screening. A total of 1520 high-risk participants aged 50 years or older were enrolled and received five scans for 4 years. Non-calcified nodules were detected in 51% of participants at the baseline screening and in 73.6% after the fifth annual screening. Of the non-calcified nodules, 61% were 4 mm or smaller in diameter. Lung cancer was detected in 66 participants with 68 lesions. Sixty-five percent of prevalent and 62% of incidence cancers were stage IA. Ten participants (18%) underwent surgical procedures for benign nodules that had been detected by screening. Screening high-risk individuals with LD-CT detected early-stage lung cancer but also detected a large number of non-calcified nodules that required periodic follow-up scans.

Toru Nakagawa, MD, (Hitachi Health Care Center, Japan) presented the 6-year experience on LD-CT screening at the Hitachi Electric Co. Ltd. Among 12,645 individuals, 60 lung cancers were surgically diagnosed (0.47%). Of these tumors, 90% were pathologically stage I. Annual repeat screening was performed for 24,889 subjects, and 22 lung cancers were detected. The detection rate was 0.09%, and all were pathologically stage I. Dr. Nakagawa stressed that repeat screening for the same cohort would be a powerful tool with which to study the efficacy of a screening method like LD-CT (Figure 2).

There were two other presentations on screening-related studies: one was biomarker analysis of the aggressiveness of CT screen-diagnosed tumors by Luis Montuenga, MD, (Clinica Universitaria de Navara, Spain); the other was competing causes of death in a lung cancer screening cohort by Rowena Yip, MPH (Weil Medical College of Cornell University, New York, NY).

ORAL PRESENTATIONS: TWO LARGE COHORT STUDIES FOR LD-CT SCREENING

Tomio Nakayama, MD, PhD, (Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan) presented an interim analysis of a nationally based cohort study on LD-CT screening from the JLCSS group. This is a non-concurrent cohort study with a control arm of participants receiving a chest radiograph. Eligible subjects were aged more than 40 years and were never screened by LD-CT, excluding patients who had been diagnosed with or were thought to have lung cancer. The subjects who received LD-CT or a chest radiograph as screening from 1995 to 2002 were enrolled. The

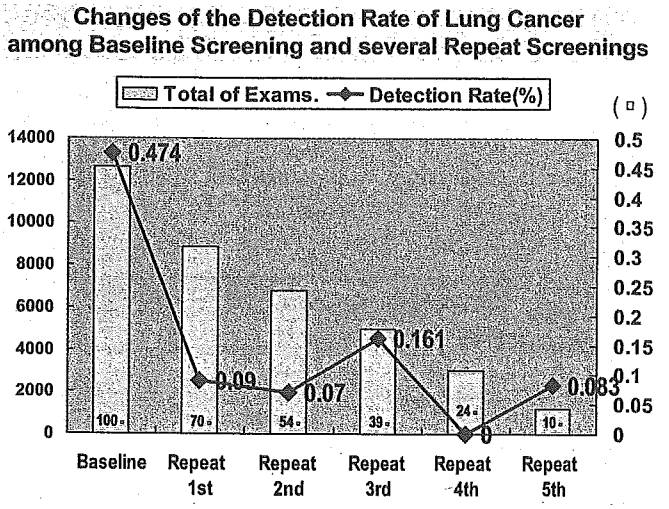

FIGURE 2. Toru Nakagawa, MD (Hitachi Health Care Center). Changes of the detection rate of lung cancer at the baseline screening and repeat screenings.

study began in 2001, and the final analysis will be performed in 2007. The sample size is an estimated 40,000 subjects for the LD-CT cohort and 80,000 subjects for the usual chest radiograph screening cohort to detect a 30% reduction of lung cancer mortality where the effect of usual screening is 30% and the pure effect of LD-CT screening is 51% ($\alpha = 0.05$, $\beta = 0.2$ two-sided test). The age of both groups is 40 to 74 years old, and follow-up period is 5 years. From nine screening groups in different districts of Japan, a total of 46,733 subjects were enrolled as the LD-CT group and 91,970 subjects as a control group. In six screening groups, the subjects were enrolled as a community-based screening and included a large number of female nonsmokers (Table 1). The detection rate of lung cancer in the LD-CT group was 0.69% in men and 0.64% in women: 3.6 and 9 times higher than those of the chest radiograph group, respectively. In repeated screenings, detection rates in the LD-CT group decreased to 0.08%. The rate of stage IA screen-detected lung cancers was 83% and 91% in baseline and repeated screenings, respectively. Currently, 850 deaths from all causes have been identified in the LD-CT screening group versus 3480 deaths in chest radiograph group, compared with 85 lung cancer deaths in the former group and 336 deaths in the latter group. In preliminary analysis, the discrepancy between overall mortality and lung cancer mortality of the cohort became gradually larger in men; however, it was not statistically significant (Figures 3).

TABLE 1. Performance of Lung Cancer Screening in JLCSS

	CT screening cohort		Usual screening cohort	
	Male	Female	Male	Female
Detected lung cancer (*n*)	216	112	64[a]	36[a]
Detection rate (%)	0.73	0.65	0.19*	0.07†

From the presentation by Tomio Nakayama, MD. CT, computed tomography; WHO, World Health Organization. [a] Lung cancer cases of the usual screening cohort are not applicable. *$P < 0.05$. †$P < 0.001$.

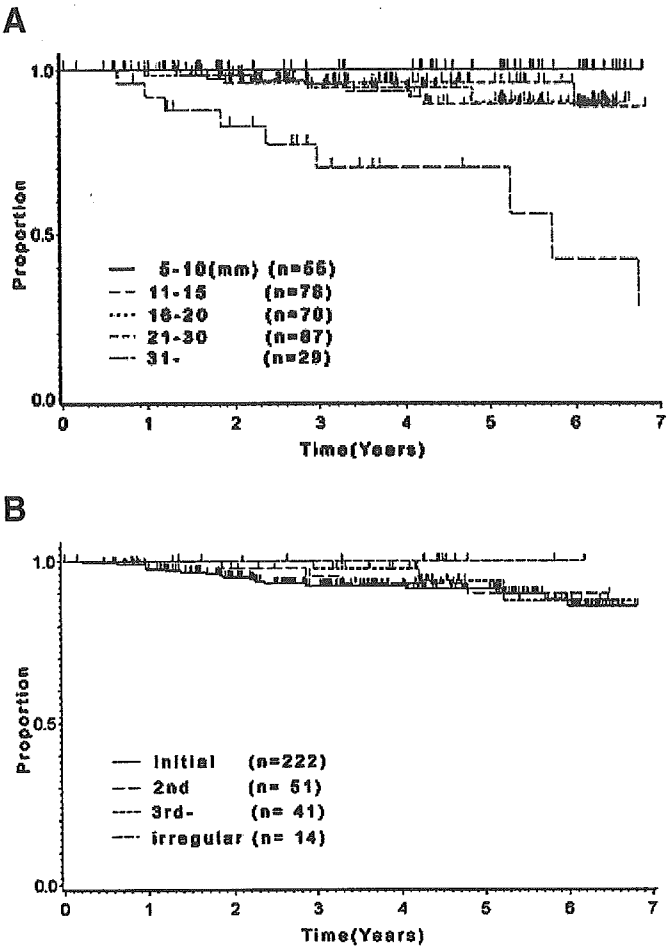

FIGURE 3. Tomio Nakayama, MD. *A*, Survival of patients with LD-CT–screened lung cancers by size (JLCSS). *B*, Survival of patients with LD-CT–screened lung cancers by cycles of screening (JLCSS).

Data with the lung cancer-specific mortality rates for each cohort, together with all caused mortality, will be presented as a final analysis in 2007. As a subset analysis, a significant difference in survival among subjects with LD-CT–detected lung cancer was found depending on the tumor size. Subjects with tumors smaller than 1 cm had better survival than others, and subjects with tumors larger than 3 cm had the lowest survival rate.

Claudia Henschke, MD, PhD, (Weil Medical College, Cornell University) reported the summarized data of the 6-year I-ELCAP project.

The ELCAP approach consists with two parts. Part A is a diagnostic mission, whereas Part B is a prognostic mission. In Part A, lung cancer distribution, such as stage, size, etc., will be clarified using the data obtained from baseline and annual repeat screenings. In Part B, the fatality rates of patients with screen-detected lung cancer, treated or non-treated/delayed treatment will be clarified specific to stage and size.

The mission of I-ELCAP is to advance policy-relevant research on the early diagnosis of lung cancer and to foster translation of up-to-date evidence into guidelines for practice. The advantage of the I-ELCAP research approach is multifaceted. It should further state-of-the-art screening research and clinical practice, it should provide for continual updating in light of advancing knowledge, and result in incorporation of technologic advances as they develop. I-ELCAP has accumulated 28,689 baseline CT screenings and 20,706 annual repeat CT screenings at 38 institutions throughout the world. Under the systematic protocol, 253 lung cancers and 31 lung caners have been diagnosed at the baseline screening and annual repeat screening, respectively.

The median diameter of screen-diagnosed lung cancer was 15 and 8 mm in baseline and repeat screening, respectively. More than 80% of screen-detected lung cancers were stage I. A diagnostic performance biopsy proved malignancy in more than 90% of patients. Non-solid type tumors showed no size-stage relationship, whereas solid and semi-solid type tumors did. I-ELCAP revises the protocol considering these results and continues to accumulate new subjects and follow-up.

Curability can be calculated as fatality rate (FR) of untreated minus FR of treated divided by FR of untreated. In x-ray screening, the curability of stage I x-ray screen-diagnosed cancers is estimated to be 67%. According to the SEER database, curability of stage I lung cancers is estimated to be 71% in tumors 15 mm or smaller in diameter and 67% in those 16 to 25 mm in diameter. Curability of screen-detected stage I lung cancer in CT screening is estimated to be 97% if the tumor is a solid nodular type. The percentage of deaths that can be prevented by CT screening is estimated to be 81% (95% CI, 75–87%), whereas deaths prevented by chest x-ray screening is estimated to be 20% and, for those receiving normal care in America, is estimated to be only 5%, according to the 2005 report from the American Cancer Society.

Using the results of I-ELCAP, one can estimate a risk assessment model and the values for decision making regarding CT screening. For instance, a 55-year-old man who smokes more than 30 pack-years has a probability of detection of stage I lung cancer by CT screening of approximately 80%.

General discussion focused on estimation of overdiagnosis as 10% in LD-CT screening, especially involving localized pure ground-glass opacity or non-solid nodules in female nonsmokers, and the necessity of risk-benefit assessment of LD-CT screening. In the case of lung cancer showing solid or part-solid nodules on CT images, the ratio of overdiagnosis may be small. Additional data on the natural course of non-solid nodules should be accumulated.

ORAL PRESENTATIONS: EARLY DIAGNOSIS

Masahiro Kaneko, MD, (National Cancer Center Hospital, Tokyo, Japan), reviewed the history of CT and discussed future progress of CT equipment and diagnostic systems for screening. He stressed rapid advance in software development of CAD and characterization in the field of LD-CT screening. Screening systems applicable to both peripheral and hilar lesions using rapidly reconstructed LD-CT images will be desirable. Less invasive and more accurate

diagnostic intervention for LD-CT–detected nodules should be developed. Virtual bronchoscopy and three-dimensional reconstructed CT images will be potentially useful in performing accurate bronchoscopic biopsy of small peripheral lesions detected by using LD-CT screening, Progress in automated diagnostic support using CAD is mandatory for LD-CT screening.

Takashi Terauchi, MD, (Research Center for Cancer Prevention and Screening, National Cancer Center Hospital, Tokyo, Japan) discussed difficulties in using 2-[^{18}F]fluro-2-deoxy-D-glucose (FDG)-positron emission tomography (FDG-PET) scan for cancer screening. In Japan, more than 60 groups introduced FDG-PET as their daily practice-based opportunistic screening. FDG-PET is a convenient tool for whole-body screening to detect malignancy, but its accuracy is influenced by many factors, such as the size and biological behavior of tumor and the diabetic state of the subject. FDG-PET is not currently justified as a tool of cancer screening. Dr. Terauchi commented that the detection rate of cancer was up to 5% in his preliminary whole-body screening project for 3000 subjects 50 years of age or older, conducted with the approval of the institutional review board of the National Cancer Center in Tokyo. He will continue with follow-up on the same cohort for 10 years with multimodality repeated screening protocol.

Masami Sato, MD, (Miyagi Cancer Center, Japan), presented the results of population-based screening with chest radiograph and sputum cytology, which was conducted in the Miyagi prefecture in the 1990s. They applied an improved method for staining sputum samples from high-risk groups. He stressed the importance of sputum cytology for high-risk groups because the rate of Japanese smokers is still high: 42% of men and 10% of women for the overall population, and 56% and 20%, respectively, in the younger generation. However, there has been a decrease in the number of hilar-type lung cancers. He added that overdiagnosis of occult hilar-type lung cancers was very rare, according the long-term follow-up data from this group.

David Carbone, MD, PhD, (Vanderbilt University) discussed the identification and application of molecular signatures to the diagnosis and treatment for lung cancer. Using matrix-assisted laser desorption/ionization mass spectroscopy, tumor-specific proteins were characterized with small tumor samples. In his proteomics study, 57 proteins were characterized for the discrimination of malignant phenotypes with a sensitivity of 66% and specificity of 99%. Proteomics show useful information as response and prognostic indicators for patients with lung cancer. Studies on the relationship between proteomics and response/resistance to molecular-targeted drugs such as epidermal growth factor receptor and thyrosine kinase inhibitors are advancing. Proteomic patterns obtained directly from serum of nanogram amounts of fresh frozen human lung tumor tissue may allow the classification and prediction of histological groups, as well as nodal involvement and survival in resected non-small cell lung cancer. He displayed a map of whole-body protein analysis showing organ-specific patterns of protein distribution with array-like display of peaks of mass spectroscopy.

Kiyoshi Yanagisawa, MD, PhD, (Nagoya University, Japan) presented protein expression profiles in non-small cell lung cancer, on which he is working with Dr. David Carbone. They were able to obtain more than 2600 mass spectroscopy peaks from histologically selected regions of single frozen sections from 174 resected human non-small cell lung cancer and 27 normal lung tissues. They found 15 protein patterns as prognostic indicators of non-small cell lung cancer. In preliminary studies, proteomics has been shown to discriminate malignant from benign lesions using serum samples. Currently, they have identified dozens of molecular marker proteins of interest using reverse-phase high liquid chromatography followed by sequencing of peptides with an liquid chromatography tandem mass spectroscopy instrument. With further progress of proteomics research, Dr. Yanagisawa mentioned the possibility of identifying each target protein and characterizing the risk factors for specific subgroups and applying early detection of lung cancer in each molecularly characterized subgroup.

SURGICAL TREATMENT FOR SMALL LUNG CANCER

Kenji Suzuki, MD, (National Cancer Center Hospital, Tokyo) presented a prospective study for peripheral lung cancers 2 cm or smaller in diameter. His group chose a surgical procedure depending on findings of thin-section high-resolution (TSHR) CT images. The CT findings were classified as non-solid, part-solid, semi-consolidation, and solid depending on the ratio of the area of ground-glass opacity lesions on TSHR CT images. The end point of this study was local recurrence and prognosis. From 1998 to 2004, they performed surgery in 274 cases with ground-glass opacity features. They had a reference protocol by which a patient with a non-solid lesion 1.5 cm or larger in diameter would immediately undergo surgery; otherwise, patients would be monitored with TSHR CT every 3 months. Eighty-eight patients showed pure ground-glass opacity or non-solid lesions on TSHR CT images. Of these, 53 patients were female, and the median age was 63 years. Among the 54 lesions smaller than 1 cm, only one increased in size; another one disappeared and the others were stable. Among the 35 lesions 1 cm or larger in diameter, 43% increased in size or changed in density. Of the patients, 10% had a history of lung cancer, and most had tumors that increased in size, which indicates that those lesions might be metastases instead of double primary cancer. Examination of the surgical margin would not be meaningful in case of non-solid lesions; histopathological diagnosis of invasiveness seemed more important for these lesions. Lung cancers showing ground-glass opacity features on high-resolution CT images tend to have a less invasive nature. Limited surgical resection might be suitable for selected patients.

Ken Kodama, MD, (Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan) presented the results of a prospective phase II study evaluating alternatives to resection as early intervention for small peripheral lung cancer from a single institute. Eligible patients exhibited peripheral lung cancer with c-T1N0M0 with primary lesions 2 cm or

smaller in diameter. The percentage of ground-glass opacity area on high-resolution CT images (50% as a cutoff value) was applied as a new indicator for selection of a surgical procedure. From 1997 to 2004, 179 patients were enrolled in this study. Preoperative factors such as size, location, and percentage of the ground-glass opacity area on the HRCT were used as additional indicators for determining the type of lung resection (wide wedge resection, segmentectomy, or lobectomy). Other indicators from high-resolution CT findings (percentage of ground-glass opacity in tumor and intraoperative lavage cytology of the resection margin) were also considered when making decisions regarding surgical procedure. He concluded that this management algorithm seems to be feasible for preventing both local recurrence and excessive resection of normal lungs.

Nasser Altorki, MD, (Weil Medical College of Cornell University, New York, NY) summarized the results from 333 patients who underwent surgery in 35 institutes as a cooperative study of the I-ELCAP. More than 50% were female, and 63% had tumors smaller than 1.5 cm in diameter. Histologically, 65% were adenocarcinoma and more than 80% were pathologically stage IA. Less than 5% and 8% of patients had pathologically N1 and N2 diseases, respectively. Of the patients, 10% showed multiple lesions. One third of the patients had non-solid or part-solid lesions, most of which were 1.5 cm or smaller in diameter.

NON-SURGICAL TREATMENT

Fumio Imamura, MD, (Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan) presented their experience of brachytherapy for peripheral lesions through 21G percutaneous needles through applicators using ^{192}Ir. They had 12 patients and irradiation of 20 Gy/fraction (Gy/fr) in all percutaneous brachytherapy. The schedule was gradually hypofractinated 5 Gy/fr for five times to 12.5 Gy/fr for two times in transbronchial brachytherapy. The local control rate was up to 88%, and the estimated 5-year survival of these patients was more than 60%. Brachytherapy in both routes was feasible, with mild adverse reaction, such as focal radiation pneumonitis and one mild pneumothorax. Dr. Imamura discussed his experience of conformal radiation therapy among 43 patients with T1-T4N0M0 lung cancer for 4 years in a single institute. It was not a randomized controlled trial, but the patients' response to conformal irradiation was comparable to those with brachytherapy, but the former resulted in severe radiation pneumonitis in some patients. Although the application of brachytherapy for lung cancer is still limited, it may be a treatment of choice for selected peripherally located C-T1N0M0 lung cancer.

Peter Littrup, MD, (Karamanos Cancer Institute) presented his experience of the treatment of peripheral lung tumors, including metastatic nodules, using percutaneous microwave and radiofrequency ablation. Three probes cover a larger lesion without intolerable complications. Pneumothorax occurred in 36% of subjects, but only 12% required tube drainage. He also discussed the application of cryosurgery for peripheral tumors. Although the exact mechanism of local control achieved with cryosurgery has not been elucidated, this method seems to be less painful and relatively safe for a nodule adjacent to a large vessel; therefore, it has the potential for use without major complications. However, further study and longer follow-up of treated patients are needed for this technique to become more widely available.

Masafumi Kawamura, MD, (Keio University, Japan) summarized the results of treatment for metastatic pulmonary nodules using cryoablation under local anesthesia. With a percutaneous approach through CT-guided needles, two to three cycles of cryosurgery were effective in treating metastatic nodules. Histologically, the structure of pulmonary parenchyma was preserved after cryosurgery in animal experiments. Cryosurgery could avoid fatal vascular hemorrhage with modulation of depth and direction of inserted probes. It might be achievable to treat lesions in segmental bronchus. In Dr. Kawamura's phase II study, eligibility factors were five or fewer metastatic lung tumors smaller than 3 cm in diameter and performance status of 0 or 1 without metastasis in other organs. Among 20 patients, nine had two or more nodules, and the local control rate was greater than 80%. Mild pneumothorax, pleural effusion, and hemoptysis were transient complications. One patient had irreversible phrenic nerve palsy, and one had tumor implantation. Dr. Kawamura summarized that percutaneous transthoracic cryoablation with local anesthesia seemed to be feasible and that the best candidates for this method would be patients with nodules smaller than 3 cm in diameter without other metastases in other organs.

Masayuki Baba, MD, (Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Science, Japan) presented the results of clinical trials for patients with stage I peripheral non-small cell lung cancer using charged heavy particles (carbon ion radiotherapy). From 1994 to 1999, this group conducted a phase I/II trial for stage I non-small cell lung cancer using carbon ion radiation monotherapy. An optimal dose of 90 GyE in 18 fractions over 6 weeks and 72 GyE in nine fraction over 3 weeks were tolerable and achieved 95% local control with minimal pulmonary damage. In the successive phase II study, 129 patients with 131 lesions received this treatment from 1999 to 2004. Two third of the nodules were adenocarcinoma, and 72 lesions were 3 cm or smaller in diameter. Using four portals, this group studied feasibility of different fractions. They applied 72 GyE in nine fractions over 3 weeks, or 52.8 GyE for stage IA and 60 GyE for stage IB over 1 week. A respiratory-gated irradiation system was used in each patient. The local control rate was 92% in adenocarcinoma and 78% in squamous cell carcinoma. The 5-year survival rate was 54.7% and 46.1% in T1 and T2, respectively. Adverse reactions were tolerable, and carbon ion radiation therapy is considered a valid alternative to surgery for stage I non-small cell lung cancer.

Minoru Uematsu, MD, (Keio University, Japan) presented CT-guided stereotactic radiation therapy without patient breath-holding. In his previous study, positioning error of this method was shown to decrease to within 5 mm with shallow breathing and oxygen support. From 1994 to 2004, 100 patients with stage I non-small cell lung cancer were

treated using this method; half had tumors 3 cm or smaller in diameter. Histologically, 67% were adenocarcinoma and 26% were squamous cell carcinoma. Half were inoperable because of poor organ function, and the rest did not elect to undergo surgery. Radiation was 50 to 60 Gy in five to 10 fractions for 1 to 2 weeks. The 5-year survival rate was 50% in this study. There was only one treatment-related death, a 70-year-old man with squamous cell carcinoma of hilar-type and hemoptysis caused by bronchopulmonary fistula. Stereotactic focal high-dose radiation therapy was feasible for stage I lung cancer and has been covered by national insurance in Japan since 2004. This group is trying to develop a beam chasing system instead of gating to minimize movement of breathing and concentrating the radiation beam to target the lesion.

Laurie Gasper, MD, (University of Colorado Health Science Center) presented a summary of the I-ELCAP patients who were treated with radiation therapy. There were 29 patients (7% of all I-ELCAP patients) who underwent radiation therapy. Half were female; the mean age was 70 years; and mean smoking history was 45 pack-years. All received radiation therapy because of poor organ function. The 2-year disease-specific survival was 89%, and follow-up is continuing. In her literature review, Dr. Gasper cited 2-year survival rates of 30 to70% among patients with stage I or II non-small cell lung cancer who received radiation therapy alone or a combination of radiation and chemotherapy or surgery. Further studies of radiation dose and effectiveness of combined modalities are warranted.

PATHOLOGY

Masayuki Noguchi, MD, (Institute of Basic Science Research, University of Tsukuba, Japan) summarized the results of the consensus meeting for bronchioloalveolar carcinoma (BAC) that was held in New York, NY last year. The definition of BAC is a noninvasive lesion-preserved elastic frame of lung parenchyma. At the consensus panel, 10% of test samples with pure BAC could be diagnosed in agreement. Dr. Noguchi proposed that the World Health Organization histological subclassification of pulmonary adenocarcinoma should be revised as part of BAC. Pure BAC is a noninvasive lesion and should be included as a preneoplastic entity instead of adenocarcinoma. Most lesions that are part-solid type on CT images were diagnosed as adenocarcinoma mixed with BAC components. Radiological and pathological correlation studies revealed that pure ground-glass opacity in high-resolution CT images correspond to BAC features in histology. The biological behavior of adenocarcinoma is related to the ratio of the area of BAC (replacing the alveolar epithelium) and the area of solid component (with fibroblasts infiltration or with scar formation) in a lesion, which indicates the ratio of ground-glass opacity radiologically. The correlation between TSHR CT images and histology is shown in Table 2. A pathologist can determine whether the lesion has BAC components in a resected specimen, but it is difficult to determine the ratio of BAC component in a whole lesion. TSHR CT images will be able to visualize the ratio of ground-glass opacity easily using a three-dimensional reconstruction technique.

Adi Gazdar, MD, (University of Texas Southwestern Medical Center) presented endothelial growth factor receptor (EGFR) family mutations in the pathogenesis of lung cancer. The mutation of TK domain of the EGFR targets specific subpopulations of non-small cell lung cancer; that is, adenocaricnoma histology, non-smoker status, East Asian ethnicity, and female gender. Gene amplification and amplification mutation of other family members such as HER2, EGFR3, and EGFR4, as well as downstream signaling pathway genes, including k-RAS and b-RAF, may have important roles in the evolution of adenocarcinoma. Mutations in EGFR and HER2 are the first known molecular changes that target lung cancers arising in non-smokers. These mutations are found in both peripheral adenocarcinoma and their precusor lesions atypical adenomatous hyperplasia. They are absent in hilar-type adenocarcinoma such as bronchial gland tumors. Mutations in k-RAS and b-RAF have often been shown in adenocarcinoma of smokers. The molecular pathways to lung cancers in smokers and non-smokers may be different. The mutation status of EGFR correlates partly to sensitivity and resistance to EGFR TK inhibitors. Understanding the biological mechanism and role of these gene mutations will lead to the improved selection of patients to treat effectively and to find preventive interventions for the high-risk population for adenocarcinoma of the lung.

TABLE 2. Correlation of Radiologic-Pathologic Findings with Small Peripheral Adenocarcinoma

WHO classification	Histologic classification of small adeno-carcinoma*	TSHR CT** findings
BAC type adenocarcinoma		
Bronchioloalveolar carcinoma	Type A and B	Pure GGO
Mixed adenocarcinoma with BAC component	Type C	GGO with a solid component
Non-BAC type adenocarcinoma		Solid nodule without GGO
Acinar	Type E	
Papillary	Type F	
Solid adenocarcinoma with mucin	Type D	
Mixed adenocarcinoma without BAC component	Mixed type with D, E and F	

* Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, Kondo H, et al. Small adenocarcinoma of the lung: Histologic characteristics and prognosis. Cancer 1995; 75: 2844–52.

**TSHR CT = thin-section high-resolution CT.

Yasushi Yantabe, MD, (Aich Cancer Center, Japan) presented a new molecular classification for adenocarcinoma of the lung through surgical-pathological molecular study in his institute. Thyroid transcriptional factor-1 (TTF-1) is considered to be a key regulatory gene of normal peripheral lung parenchyma regulating functional molecules such as surfactant proteins. Dr. Yantabe addressed the concept of the terminal respiratory unit (TRU) as a common lineage representing a functional unit of a normal peripheral airway. The TTF-1–positive subtype of adenocarcinoma was found to be prevalent in women and non-smokers, and it frequently showed mutation of the EGFR. Furthermore, other molecular alterations, such as p53, K-ras, Rb, and p27/Kip2, were involved with a pattern different from other subtypes. This TRU-type adenocarcinoma is a distinct entity in molecular profiles. Adenocarcinoma from TRU showed better prognosis compared with other types of adenocarcinoma in his series. Lineage of TRU-adenocarcinoma includes atypical adenomatous hyperplasia, non-mucinous BAC, adenocarcinoma with a BAC component, and a proportion of poorly differentiated adenocarcinoma. Clinically, patient selection based on the molecular features may be useful for the diagnosis and treatment of lung adenocarcinoma.

Selection mechanisms for k-Ras and EGFR mutation depending on clinical factors such as smoking history, ethnicity (East Asian), and sex (female) were issued, and the EGFR mutation in premalignancy or in other pulmonary diseases was the focus of discussion.

In the poster session, there were 30 scientific presentations, including results and model assessment of LD-CT screenings, computer-aided diagnosis for LD-CT, PET scan for opportunistic screening, detection of coronary diseases on LD-CT screening, diagnostic interventions for CT-detected small nodules, local less-invasive treatment for CT-detected lung cancer, pathological features of small lung cancers, and the issues of overdiagnosis.

Small-group workshops focused on three topics: CT-guided, fine-needle aspiration biopsy and follow-up issues including algorithm of follow-up in negative biopsy; CAD and characterization of non-calcified nodules in LD-CT screening; and multicenter trials for LD-CT–detected small lung cancer.

The final portion of the conference was three educational seminars focused on the interpretation of LD-CT images as a diagnostic tool for screening by Shusuke Sone, MD, (Azumi General Hospital, Japan), Dorith Shaham, MD, (Hadasssh Medical Center, Israel), and Salvatore Giunta, MD, (Instituto Nazionale Tumori Regina Elena, Italy); management of small nodules detected in LD-CT screening by David Yankelevitz, MD, (Weil Medical College of Cornell University, New York, NY), Javier Zulueta, MD, (Clinica Universitaria de Navarra, Spain), Kiyoshi Mori, MD, (Tochigi Cancer Center, Japan), and Kozou Yamada, MD, (Kanagawa Cancer Center, Japan); and computer assistance in reading LD-CT images by Susan Wood, PhD, (Medicsight, UK), Gerhard Kohl, (Siemens AG, Germany), and Noboru Niki, PhD, (University of Tokushima, Japan).

We had an exciting and provocative conference in Nara, Japan, with the cherry trees in full bloom. We will make progress to the second stage of LD-CT screening and accumulate innovative scientific evidence on the diagnosis and treatment for early-stage, curable lung cancer.

Finally, we gratefully acknowledge the West Japan Thoracic Oncology Group; Tokai University School of Medicine; Medicsight (UK); Siemens (Germany); Astrazeneka (Japan); and other companies for their sponsorship of this conference.

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A Computer-aided Diagnosis (CAD) System in Lung Cancer Screening with Computed Tomography

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Abstract. *We evaluated a computer-aided diagnosis (CAD) system with automatic detection of pulmonary nodules for lung cancer screening with computed tomography (CT). Five hundred and eighteen participants were examined with low-dose helical CT during a lung cancer screening by three respiratory physicians according to the General Rule edited by the Japan Lung Cancer Society. Four cases were detected by CAD and pathologically diagnosed as lung cancer. We compared the detection capability of the physician and CAD in 301 participants. Three physicians determined 75/301 (24.9%) participants as "e" (suspicious of lung cancer) in consensus without CAD, while 3 participants were added to "e" with CAD. Three physicians did not independently judge as "e" in 14 (18.7%), 16 (21.3%) and 16 (21.3%) out of 75 participants. CAD could not identify 17 (22.7%) nodules of 75 participants, and all 17 were less than 6 mm in diameter. The CAD system offers a useful second opinion when physicians examine patients at lung cancer CT screenings.*

Few studies on lung cancer screening have been reported using low-dose helical computed tomography (CT) scanning (1-6). Helical CT scanning has the highest sensitivity for detection of pulmonary nodules compared to other examinations and has the potential to demonstrate small, clinically unapparent, curable lung cancer (2, 3). The reliable detection of small pulmonary nodules is an important task for early detection of lung cancer with low-dose helical CT because a follow-up examination can demonstrate growth as a sign of a potential malignancy (7). The sensitivity of small pulmonary nodules detected by physicians is not satisfactory (8, 9), especially at a mass screening for lung cancer.

Sufficient automatic nodule detection may be useful to guide physicians to questionable structures. There are some ways to integrate these features into the physician's work. A very convenient one is the integration of a softcopy viewing workstation. Utilization of automatic nodule detection in the clinical routine has become possible due to the dramatic increase in computer performance within acceptable limits (10-12). The Moriyama research group in Japan has developed a computer-aided diagnosis (CAD) system, which includes automatic nodule detection and a conventional viewing workstation needed to report thoracic CT examinations (10, 13, 14). In this study, we used this CAD system to detect pulmonary nodules on CT scans performed for a lung cancer screening with helical CT scan. In this report, we present the usefulness of the CAD system at a mass screening for lung cancer.

Materials and Methods

Subjects. All participants gave informed consent for CT screening of lung cancer and filled out questionnaires about respiratory symptoms, smoking and past histories. All participants were living in the surrounding areas of the National Kanagawa Hospital, Japan. From October 2001 to January 2003, a total of 518 CT screening procedures were performed. All 518 procedures were baseline screenings and there were no repeat screenings. This included 301 without CAD system assistance in the first half of the period and 217 which utilized the CAD in the second half. The

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Key Words: Lung cancer, screening, helical computed tomography (CT) scan, computer-aided diagnosis (CAD) system.

Table I. *Characteristics of participants.*

	without CAD	with CAD
Participant number	301	217
Age median (range)	60 (26-91)	54 (21-84)
Sex (male/female)	220/81	156/61
Smoking index*	785.7	766.1

CAD; computer-aided diagnosis, * cigarette counts x smoking year

characteristics of the participants are summarized in Table I. The majority of participants (72.6%) were men between 20 and 85 years old. The frequency of current or former smokers was 174 (33.6%) and 66 (12.8%), respectively.

CT scanning. A helical CT scanner [Xvision/SR (TSX-002A), Toshiba, Japan] was used for this study. The scanning parameters were 120 kilovolt peaks, 50 mA, 10-mm collimation and 2.0 pitches. The whole lung field was scanned and completed at deep inspiration during a single breath-hold of about 15 sec. The total time between entering and leaving the room was only about 10 min. Ten-millimeter reconstructed images were stored on optical disks (650 megabytes of volume per disk). After scanning, high resolution CT (HRCT) scanning was added on the same day, when the lesion was strongly suspected of being lung cancer. The scanning parameters of HRCT were 120 kilovolt peak, 150 mA 2-mm collimation and 1.0 pitch reconstructed images at the HRCT scanning.

CAD workstation. The Moriyama research group kindly provided us with the CAD system they had developed. The hardware of the CAD system consists of a Toshiba AS 7000 U5 workstation (10, 14). A screenshot of the CAD system's user interface is shown in Figure 1. This CAD system is equipped with automatic image diagnosis and an image screening function. When the automatic image diagnosis process is started in advance, the physician can begin lung cancer diagnosis at any time. Four continental slice CT images are always displayed and the physician can easily search the chosen image. When the physician clicks the mouse button on the image, the marker displays at the position of the cursor. The diagnostic results from all subjects are recorded on the hard disk drive. Network transfer of CT data from the CT scanner to the CAD workstation is realized with DICOM protocol. The CAD software includes a detection algorithm for pulmonary nodules and a user interface. The detection algorithm includes a complex segmentation of lung parenchyma (deletion of the CT table and soft tissue of the chest wall), followed by detection of structures with soft tissue density within the lung parenchyma and a region analysis to evaluate detected structures in the 3D data set (15). First, soft tissue objects within the segmented lung borders are detected using a fixed density threshold value (approximately –600 Housefield Units [HU]). Evaluation is done after using a 3D region-growing algorithm. Objects with a detected volume of less than 10 voxels are ignored. A spherical soft tissue density nodule this size corresponds to a diameter of approximately 5 mm due to the partial-volume effect and density threshold value. For the remaining objects, the distinction between probable nodules and other structures (especially vessels and scars or subsegmental atelectasis) are based on object geometry, especially on the length/width/height ratio, because it can be assumed that vessels and scars have a non-spherical shape.

Interpretation. All images were obtained at window settings appropriate for lung parenchyma (level, -600 HU; width, 1800 to 1600 HU). As for the CAD's performance, the time required to obtain images and diagnose them was about 7 min, but the CAD cannot simultaneously obtain images from a CT scan when a CT scan is running another thoracic examination. Three respiratory physicians separately interpreted all cases according to the General Rule for the Clinical and Pathological Record of Lung Cancer edited by the Japan Lung Cancer Society (16). We made a judgement without CAD system assistance in the first half. In the second half, we used the CAD system and three physicians separately interpreted initially and then made a final judgement with CAD assistance (Figure 2). When they could not reach a consensus, a final conclusion on the findings was reached by consensus at the conference.

Results

Between October 2001 and January 2003, lung cancer screening with helical CT scan was performed on 518 participants (376 men, 142 women; age range 20-85 years, mean age 57.9 years). The three respiratory physicians made judgements in consensus according to the General Rule for the Clinical and Pathological Record of Lung Cancer (the Japan Lung Cancer Society) ("a", undetermined; "b", within normal limit; "c" old inflammatory lesion; "d", suspicion of disease other than lung cancer; "e", suspicion of lung cancer). We made judgements for 301 participants without the CAD system in the first half and for 217 participants with the CAD system in the second half.

In the first half, 75/301 (24.9%) participants were determined as "e" without CAD, while 55/217 (25.3%) participants were "e" with the CAD system in the second half (Table II). Four participants were histopathologically diagnosed with lung cancer in all periods. The sizes of four lung cancer cases were 9 x 9 mm, 18 x 15 mm, 32 x 20 mm and 50 x 45 mm in diameter. One case with a lesion 9 x 9 mm in diameter was diagnosed with pathologically bronchioloalveolar carcinoma. Besides lung cancer, other pulmonary diseases were diagnosed such as active pneumonia, non-tuberculous mycobacterium infection, bullae and chronic obstructive pulmonary disease.

The diagnosis by each physician of 301 cases in the first half is shown in Table III. The judgements of "e" by three physicians (Dr. A, Dr. B and Dr. C) were 62 (20.6%), 54 (17.9%) and 61 (20.3%), respectively. Three physicians determined 75/301 (24.9%) participants as "e" in consensus

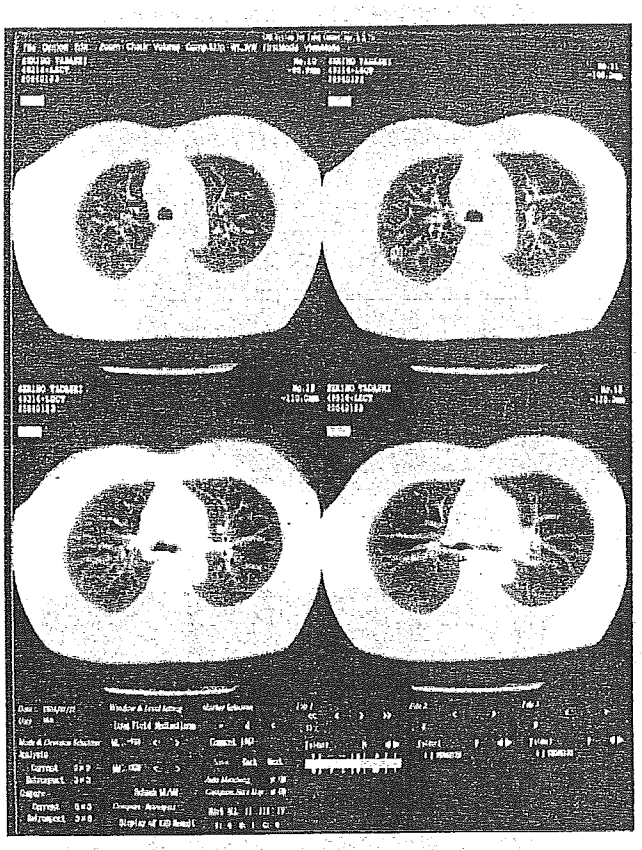

Figure 1. *Screenshot of the CAD system's user interface.*

Table II. *Judgements of participants.*

	without CAD	with CAD
Participant number	301	217
Judgement*		
b/c/d/e	73/29/124/75	56/36/70/55
% e	24.9%	25.3%

*We made judgements according to the General Rule for the Clinical and Pathological Record of Lung Cancer (the Japan Lung Cancer Society: "b", within normal limit; "c" old inflammatory lesion; "d", suspicion of diseases other than lung cancer, "e", suspicion of lung cancer). The three respiratory physicians judged in consensus.

without CAD. All three physicians independently judged as "e" 46/75 (61.3%) participants, while one or two physicians judged 29 other participants as "e". We re-evaluated 301 participants and judged them with CAD. With CAD, three participants were added to "e" from other judgements in the first half without CAD. These three nodules were 8 mm, 5 mm and 5 mm in diameter. CAD picked up three cases overlooked by all three physicians, one nodule being 8 mm in diameter and highly suspicious of early lung cancer (Figure 3A). All 4 participants, who were histopathologically diagnosed as lung cancer, were detected by CAD.

Three physicians determined 75/301 participants as "e" in consensus without CAD. Three physicians did not independently judge as "e" 14 (18.7%), 16 (21.3%) and 16 (21.3%) of the 75 participants, respectively. CAD could not identify 17 (22.7%) nodules of the 75 participants (Figure 3B). Ten of the 17 nodules were diagnosed as "e" by all 3 physicians, while 7 other nodules were diagnosed by one or two physicians (2 nodules were diagnosed by one physician and 5 nodules by two physicians). All 17 nodules were less than 6mm in diameter: ≤6mm and >5mm, 8 nodules; ≤5mm and >4mm, 4 nodules; ≤4mm and >3 mm, 5 nodules (Figure 4). No apparent characteristics of CT number were noted in these 17 tiny nodules. Four nodules out of 17 were adjacent to the pleural lung surface and another four nodules were adjacent to the vessels.

Discussion

In this study, we evaluated a computer-aided diagnosis (CAD) system at a lung cancer CT screening. Three physicians determined 75/301 (24.9%) participants as "e" (suspicious of lung cancer) in consensus without CAD, while 3 participants were added to "e" with CAD. Three physicians did not independently judge as "e" 18.7%, 21.3% and 21.3% of the 75 participants, while CAD could not identify 22.7% of the nodules of the 75 participants. The CAD system may provide a useful second opinion at lung cancer CT screenings, despite its limited sensitivity.

The CAD system is able to demonstrate some nodules overlooked by the physicians because they were located in more central areas of the lung. In this study, 3 cases were overlooked by all three physicians and reassessed to an "e" judgement with CAD assistance. One of these three was 8 mm in diameter and highly suspicious of early lung cancer. All three physicians might have overlooked this case because of a faint shadow located in the subpleural lesion. Midthun *et al.* reported that 21% of nodules 8-20 mm in size were malignant and that lesions 8-20 mm in size require further evaluation (17). We must make further examinations in this case.

On the other hand, the CAD system has an obvious weakness in the detection of nodules adjacent to the pleural lung surface because the image segmentation algorithm recognizes the nodule as a part of the chest wall and excludes it from further image processing. The algorithm is designed to detect nodules with diameters of at least 5 mm (10, 14). All 17 tiny nodules, detected by physicians and not identified by the CAD system, were less than 6 mm in our results. Four of the 17 nodules were adjacent to the pleural lung surface

Table III. *Judgements of 301 participants by each of the three physicians.*

Judgement*	Dr. A	Dr. B	Dr. C
b/c/d/e	82/31/126/62	91/46/110/54	99/38/103/61
% e	20.6%	17.9%	20.3%

*We made judgements according to the General Rule for the Clinical and Pathological Record of Lung Cancer (the Japan Lung Cancer Society: "b", within normal limit; "c" old inflammatory lesion; "d", suspicion of diseases other than lung cancer, "e", suspicion of lung cancer). The three respiratory physicians (Dr. A, Dr. B and Dr. C) independently judged the 301 participants.

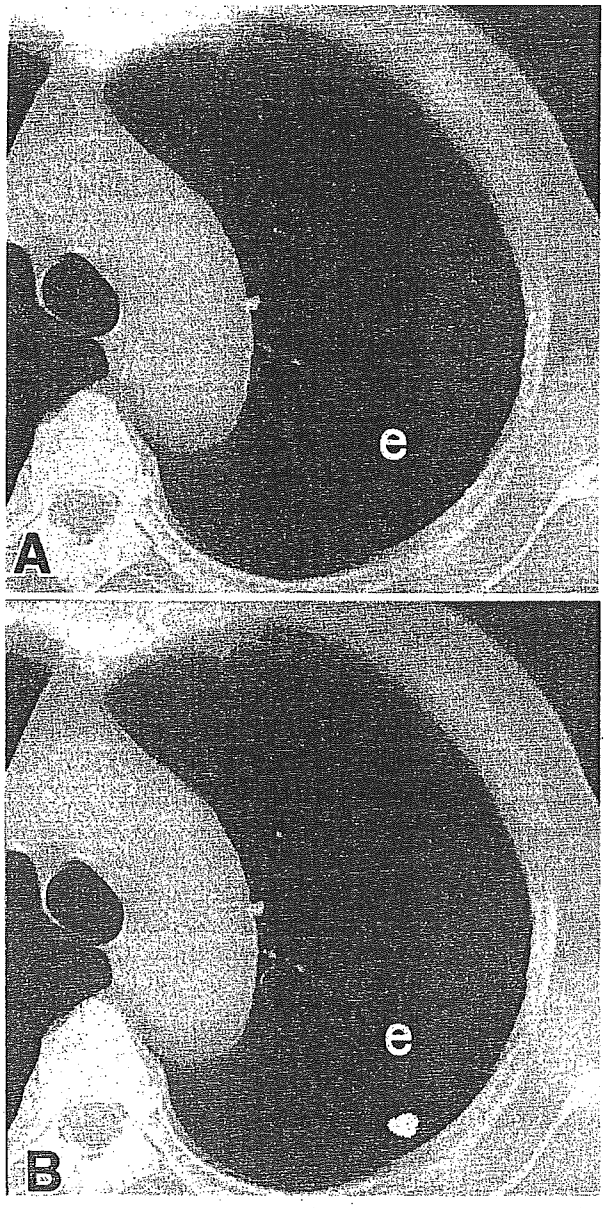

Figure 2. *The detection of pulmonary nodules by CAD. (A) Original image of the location. (B) Detection results- a lesion was detected by the CAD system.*

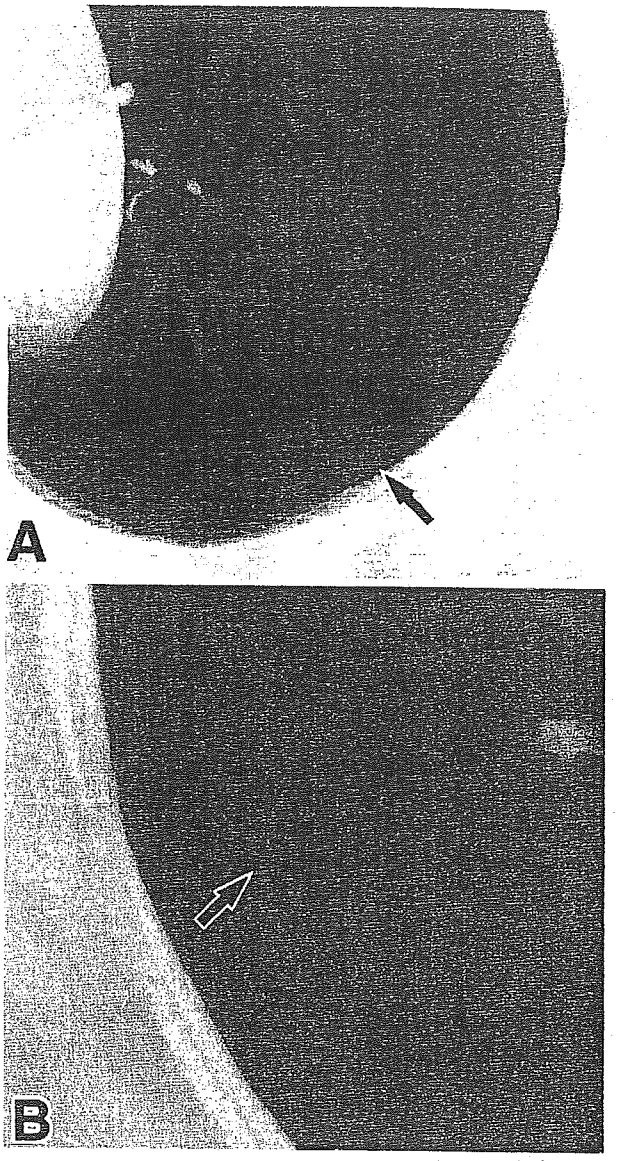

Figure 3. *(A) Small pulmonary nodules detected by CAD without the physicians' detection were 8 mm in diameter and –709 Housefield Units (HU) in CT number. (B) CT scan revealed a pulmonary nodule (5 mm, CT number –720 HU) detected by physicians but one that CAD could not identify.*

and the other four were adjacent to the vessels. Many pulmonary nodules including grand glass opacity (GGO) were picked-up by the helical CT scan (1), and a part of GGO is thought to be pulmonary adenocarcinoma at an extremely early stage (18). The General Rule for Clinical and Pathological Record of Lung Cancer edited by the Japan Lung Cancer Society notes that further examinations are necessary for cases with nodules more than 5 mm in diameter in helical CT screening for lung cancer (16). Further analysis will reveal the standard pick-up size of small nodules.

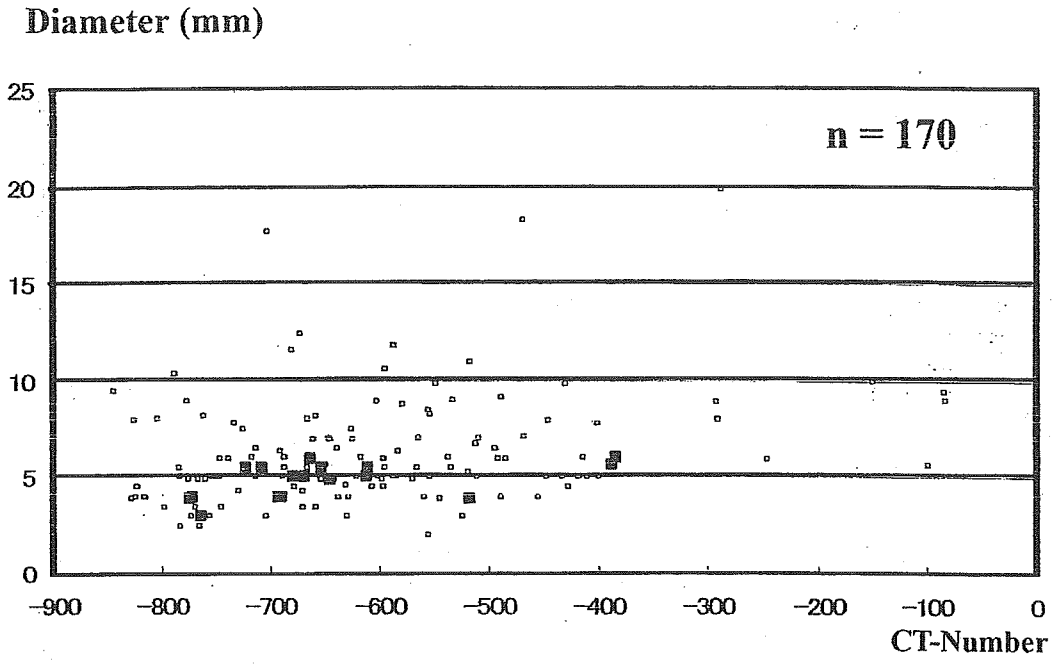

Figure 4. *Characteristics of small pulmonary nodules. CAD could not identify 17 nodules (closed square) detected by physicians. Many other nodules (total 170 nodules, open circle) were detected both by physicians and the CAD system. All 17 nodules were around or less than 6 mm in diameter. No apparent characteristics of CT number were noted in these 17 nodules.*

The CAD system for the analysis of pulmonary nodules has the following advantages: (1) great speed of numerical calculation, allowing precise, quantitative and reproducible measurements, (2) an ever-increasing knowledge base to provide diagnostic information, and (3) non-susceptibility to fatigue (11). Armato *et al.* reported that 84% of missed cancers in a database of low-dose CT scans were detected correctly with the CAD system (19). Great benefits may well be seen in the quantitative results that can be derived from the analysis of a large number of subjects in a reproducible, efficient manner. These characteristics are very adequate for mass screenings for lung cancer. In this study, the "e" judgements determined by three physicians varied from 17.9% to 20.6% in the reevaluation of participants. The coincidence of all three physicians in "e" participants was not particularly high at 61.3%. The CAD system may provide physicians with tools to obtain more accurate diagnoses for lung cancer (20), especially in cases diagnosed by one physician.

Lung cancer screening using low-dose helical CT scanning is still a controversial issue (21, 22). The helical CT scan has the highest sensitivity for detection of pulmonary nodules compared to other examinations (2, 3). Nawa *et al.* reported that low-dose helical CT might be a promising method for screening early lung cancer at health examinations (23). There is currently insufficient evidence to support screening for lung cancer with any screening modality (20). Well-designed clinical trials are necessary to establish the guidelines for mass screening for lung cancer (24, 25).

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