Detection of Early Lung Cancer : Results of Radiologic and Cytologic Screening in the Miyagi Program

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NAKADA, T., SATO, H., SAITO, Y. and FUJIMURA, S. *Detection of Early Lung Cancer : Results of Radiologic and Cytologic Screening in the Miyagi Program.* Tohoku J. exp. Med., 1987, **152** (2), 173-186 — Eighty-eight lung cancers including 82 primary and 6 metastatic tumors were detected by chest x-ray examination of a total of 363,320 participants in Miyagi Prefecture in Japan during 3 years period from 1982 to 1984. Sputum cytology was performed in the high-risk group (above 50 years of age with cigarette index above 600) of the total participants during the same period. This detected 67 patients with malignant tumors including 5 with cancer of the upper respiratory tract and 62 with primary lung cancer. Fifty-one of 67 cancers (82.3%) detected by sputum cytology were radiographically occult lung cancers. The annual ratio of the detection of lung cancer was 45/100,000 in the first year, however, it decreased to 38/100,000 in the second year and to 15/100,000 in the third year. Cancer resection was performed in 63.6%, 76.1% and 80.0% of the patients, in the first, the second and the third year, respectively. On the average, 57% of the patients who underwent cancer resection demonstrated early lung cancer. *Especially*, 45 of 51 patients with lung cancer detected by sputum cytology underwent tumor resection, of which 40 (89%) bore early lung cancer. ——— early lung cancer ; x-ray examination ; sputum cytology

Definitive diagnosis of lung cancer was established in 3,839 of the patients admitted to our Institute from 1952 to 1984. However, lobectomy was possible in only 1,179 (30.7%) of them. Fifty-five percent of the resected cases were Stage 3 patients, and, needless to say, the survival rate was extremely low (31.3%) (up to the end of 1980) ; the remaining 70% were afflicted with progressive lung cancers that were no longer resectable (Akaogi 1983).

This naturally urges an effort for early detection. Early detection should be planned solely for the purpose of saving patients.

Annual screening for pulmonary tuberculosis has been carried out systematically in Japan on a national scale. Taking advantage of these regular opportu-

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nities, we reviewed indirect chest x-ray films of a total of 2,766,246 inhabitants of Miyagi Prefecture from 1952 until 1972 (Suzuki 1974). During these 20 years this review allowed detection of 198 patients with lung cancers (detection ratio: 7/10,000). Lobectomy was possible in only 65 of them. The 5-year survival after resection was only 27%. This survival rate is by no means higher compared to that in patients were at our Institute and were surgically treated. Screening by sputum cytology was also carried out in 19,332 inhabitants but lung cancer was detected in none.

Screening for lung cancer commenced in 1973 at each institute not only in Miyagi Prefecture but also in the whole country. However, such separate, institute-by-institute screening occasionally encountered various vexing problems in relation to efficiency, economy and administration.

Mass screening of the general population must be efficient, accurate and economical.

When viewed internationally, skepticism seems to prevail at present for mass lung cancer screening including sputum cytology conducted by medical organizations such as Mayo Lung Project (Sanderson 1985), Johns Hopkins University (Tockman 1985) and Memorial Sloan-Kettering Cancer Center (Martini 1985). At the 25th Congress of the Japan Lung Cancer Association held in 1984, a special report proposed that promotion of lung cancer screening on a national scale in Japan was still premature (Suemasu 1984). Nevertheless, in recognition of the significance of lung cancer screening, we have endeavoured for the past several years to lay a foundation for the screening of lung cancer.

MATERIALS AND METHODS

Screening organization by the Miyagi Lung Cancer Detection Program

With the complete assistance of Miyagi Prefecture and its cities and villages and under the collaboration of Tohoku University, Miyagi Medical Association, Miyagi Branch of Tuberculosis Prevention Association and Miyagi Anti-Cancer Society, the Miyagi Council for Anti-Lung Cancer Program was organized in 1982 to promote early detection and early management of lung cancers.

Screening method and diagnostic criteria

First screening included chest x-ray and sputum cytology

Taking into consideration the example of the already existing screening system for tuberculosis which has taken root in Japan as a duty of health-conscious individuals, the program was a project intended to develop the above system into a lung cancer screening system. High rates of cooperation from the inhabitants were expected; 90% in rural districts, 50% in urban districts and 90% at places of employment. In the first screening, indirect x-rays (70 mm or 100 mm) were taken of all participants. At the same time, high-risk subjects were chosen by interview. A sputum container was distributed to them. All participants were completely exempted from all expenses. Semi-compulsory operation is important by complete financial support from the government and local self-governments. (Fig. 1)

Fig. 1.

Indirect radiography. The indirect, posteroanterior x-ray films (70 mm-100 mm) were assessed twice by 2 radiology technologists. Films suggesting abnormalities such as lung cancer, tuberculosis and other diseases were sorted out. All films suspected of lung cancer were filed together with the films of the past 2 years (for this tremendous amount of work, we are indebted to the Miyagi Tuberculosis Prevention Association).

Films placed in files were subsequently reexamined twice and interpreted by 2 radiology specialists. After examining the shadows and yearly changes, participants suspected of lung cancer were recorded as subjects requiring closer examination. In this procedure, it is important to specify the pathological details on a check up card attached to the file.

This method was considered useful in the improvement of the diagnostic accuracy, saving of expenses and thus permeation of lung cancer screening campaign.

Sputum cytology. High-risk subjects were chosen by interview, to whom a sputum container was handed.

The high-risk group consisted of subjects above 50 years of age with a cigarette index above 600 and those who had a history of hemoptysis within the past 3 months. Three day early morning sputum was pooled in the container. They were recovered for cytology as thoroughly as possible through the help of community organizations.

The sputum samples collected were processed by the modification (modified by Sato et al. 1979) of the Saccomanno blending technique (Table 1).

Specimens were prepared in duplicate. The cytology slides were scrupulously screened by 2 cytotechnologists. They were subsequently interpreted by 2 cytopathologists separately. Judgement more critical of the two was adopted in the diagnosis of lung cancer. Evaluation of the cytologic findings was based on our own criteria (Table 2). Our criteria retain compatibility to the Papanicolaou's classification.

As a principle, class III and above were recalled for closer examination. District health nurses were mobilized to recall these patients for repeat examination.

TABLE 1. *Procedure for sputum cytology by modified Saccomanno method*

1.	Pooling of 3-day sputum in a plastic jar containing 50% ethanol and 2% carbowax as fixative.
2.	Homogenization of the fixed specimens at 18,000 rpm for 30 sec.
3.	Separation of the precipitates by centrifugation at 1,500 rpm for 3 min.
4.	Suspension of the precipitates by adding fixative and vibration of the plastic jar.
5.	Preparation of specimen on a slide.
6.	Staining of air-dried slides by Papanicolaou's stain.

TABLE 2. *Diagnostic classification of sputum cytologic findings*

Unsatisfactory specimen
No atypical cell (Class I)
Atypical cells without malignant features (Class II)
Squamous metaplastic cells are classified according to the grade of atypia
◇ Mild atypia ◇ Moderate atypia ◇ Severe atypia
Suspicious cells and/or atypical cells consistent with borderline lesion (Class III*)
Malignant cells with low grade atypia and/or few malignant cell count (Class IV*)
Obviously malignant cells (Class V*)

* Requiring further examination.

Second screening (recalled subjects)

Subjects who were recalled were examined by direct radiography and usual and computed tomography. In the interpretation of these films, it is important to refer to the previous indirect x-ray films and pathological details specified, because the shadow detected in indirect x-ray films occasionally escapes detection by direct films. Cases suspected of lung cancer need diagnoses by bronchography, bronchoscopy, peripheral brushing cytology and sometimes open lung biopsy.

Subjects recalled by sputum cytology were examined by direct radiography and repeat sputum cytology. In addition, under bronchoscopic control, bronchial brushing cytology and aspiration cytology were performed. In cases in which the cytology was negative and the localization procedure failed by radiographic and bronchoscopic approaches, otorhinological examination, and further bronchoscopic and cytologic examinations together with biopsy were repeated. Localization was achieved in some cases after repeating these examinations for more than 10 times.

In cases in which lung cancer was identified, we recommended surgical intervention whenever possible. Histopathological diagnoses were also carried out.

RESULTS

Screening of the general population by a combination of indirect radiology with sputum cytology by the above-mentioned method was completely accomplished in 1982.

Screening of general population for tuberculosis and lung cancer-interpretation of indirect x-ray films

Participants in lung cancer screening by indirect x-ray in accordance with the new criteria of the Miyagi Council for Anti-Lung Cancer Program amounted to 67,754 inhabitants in 15 districts in 1982, to 120,467 in 28 districts in 1983 and to 175,099 in 37 districts in 1984. Participants in 3 years totalled to 363,320 (Table 3). From total participants, abnormal shadows were detected in 7.3% (26,668). Subjects who needed closer examination for suspected lung cancer amounted to 4.7% (17,232) of the total, for which special files of indirect x-ray films were prepared. These files were reexamined and interpreted by 2 radiology specialists. As a result, 1.8% (6,537) were found to require recalling for repeat examination.

Energetic examination of these recalled subjects resulted in detection of primary lung cancer in 23 subjects in 1982, 24 in 1983 and 35 in 1984, amounting to 82 in total. In addition, 6 metastatic lung cancers and 1 chest-wall tumor were also detected.

Lung cancer screening of general population-sputum cytology

By interview, 29,612 subjects (8.2% of total participants) were categorized in the high-risk group. A sputum container was distributed to all of them, and was recovered from 23,419 subjects (79%). Cytological diagnosis was possible in 22,713 of them (Table 4).

One hundred and seventy-six subjects suspected of lung cancer were recalled. Malignant tumors were found in 67. These included 62 primary lung cancers. Radiological examination was negative in 51 (82.3%) of lung cancers detected by sputum cytology.

TABLE 3. *Result of screening by chest x-ray in Miyagi Prefecture*

	Number of subjects			Total
	1982 15 districts	1983 28 districts	1984 37 districts	
Screened by chest x-ray	67,754	120,467	175,099	363,320
Checked abnormal shadows	5,398 (8.0%)	8,775 (7.3%)	12,495 (7.0%)	26,668 (7.3%)
Reviewed by previous films	3,927 (5.8%)	5,365 (4.5%)	7,940 (4.5%)	17,232 (4.7%)
Suspected of cancer	1,425 (2.1%)	1,816 (1.5%)	3,296 (1.9%)	6,537 (1.8%)
Detected lung cancer	23	24	35	82
Metastatic lung cancer	2	1	3	6
Chest wall tumor			1	1

TABLE 4. *Result of screening by sputum cytology in Miyagi Prefecture*

	Number of subjects			Total
	1982 15 districts	1983 28 districts	1984 37 districts	
Screened by chest x-ray	67,754	120,467	175,099	363,320
High-risk group	7,215 (10.6%)	9,790 (8.1%)	12,607 (7.3%)	29,612 (8.2%)
Sputum submitted for examination	5,858	7,802	9,759	23,419
Sputum available for diagnosis	5,580 (8.2%)	7,591 (6.3%)	9,542 (5.4%)	22,713 (6.2%)
Suspected of lung cancer	48	74	54	176
Detected lung cancer	21	23	18	62
Detected cancer of upper respiratory tract	1	3	1	5
Radiographically occult lung cancer	17 (81.0%)	18 (78.3%)	16 (88.9%)	51 (82.3%)

Diagnostic criteria of sputum cytology and establishment of diagnosis

On examining the diagnoses of lung cancer (Table 5) in accordance with the diagnostic criteria (Table 2), lung cancer was confirmed in 10 of 102 class III

TABLE 5. *Results of sputum cytology according to diagnostic classification*

	Number of subjects			Total
	1982 15 districts	1983 28 districts	1984 37 districts	
Sputum available for diagnosis	5,580	7,591	9,542	22,713
Class I	97 (1.7%)	222 (2.9%)	153 (1.6%)	472 (2.1%)
Class II	5,435 (97.5%)	7,295 (96.1%)	9,335 (97.8%)	22,065 (97.2%)
Class III	28 (0.5%) ④	44 (0.6%) ②	30 (0.3%) ④	102 (0.4%) ⑩
Class IV	8 (0.1%) ⑥	16 (0.2%) ⑪	8 (0.1%) ②	32 (0.1%) ⑱
Class V	12 (0.2%) ⑪	14 (0.2%) ⑩	16 (0.2%) ⑫	42 (0.2%) ③③
Total number of confirmed cancer	②①	②③	①⑧	⑥②
Cancer of upper respiratory tract	1	3	1	5

○ confirmed lung cancer

TABLE 6. *Number of cytologically detected patients according to cigarette index*

Cigarette index	Screened by sputum cytology	Detected lung cancer
0	218 (110)	
~ 599	365 (28)	
600~ 799	10,243 (24)	13 (0.13%)
800~ 999	6,222 (15)	21 (0.34%) (1)
1,000~1,199	2,649 (10)	14 (0.53%)
1,200~	2,934 (8)	19 (0.65%)
Unknown	82 (4)	
Total	22,713 (199)	67 (0.29%) (1)

() hemoptysis

patients and in 19 of 32 class IV patients. In 33 of 42 class V patients, the lesion was localized and confirmed as lung cancer. Judgement of class III is a delicate question.

Cigarette index and cytologically detected lung cancers

Table 6 shows the distribution of 67 cytologically detected lung cancers by the cigarette index. No lung cancer was detected in subjects with a cigarette index below 600. It was detected in 13 (0.13%) of subjects with a cigarette index from 600 to 800, in 21 (0.34%) of subjects with a cigarette index from 800 to 1,000, in 14 (0.53%) of subjects with a cigarette index from 1,000 to 1,200 and in 19 (0.65%) of subjects with a cigarette index above 1,200. The detection rate was very high in cigarette smokers. In total, it was detected in 67 (0.29%). This high detection rate was really worth the painstaking effort.

TABLE 7. *Age, sex and method of detection in 133 detected lung cancer cases*

Age	Method of detection						Total
	x-Ray only		Cytology only		Dual screen		
	Male	Female	Male	Female	Male	Female	
~49	1	5					6
50~59	4	7	10		1		22
60~69	13	8	28		3		52
70~79	19	9	10		6		44
80~	3	2	3		1		9
Total	40	31	51		11		133

TABLE 8. *Cell type and method of detection in 133 confirmed cases*

Cell type	Method of detection						Total
	x-Ray only		Cytology only		Dual screen		
	Male	Female	Male	Female	Male	Female	
Squamous cell ca.	11	3	50		9		73
Adenoca.	15	24	1		2		42
Small cell ca.	5	1					6
Large cell ca.	9	1					10
Adenosquamous ca.		1					1
Adenoid cystic ca.		1					1
Total	40	31	51		11		133

Age distribution of lung cancers

Primary lung cancers were detected in 71 by radiography alone, in 51 by sputum cytology alone and in 11 by a combination of both, amounting to 133 in total (Table 7). This indicates that sputum cytology cannot be substituted by radiography.

The subjects with detected lung cancer consisted of 102 males and 31 females. Ages above 60 were predominant.

Histological types of lung cancers detected by screening

Table 8 shows the histological types of lung cancers by the method of detection. The majority (73) of lung cancers were squamous cell carcinomas, of which 70 were found in males. The squamous cell carcinomas (59) detected by sputum cytology predominated all others. Adenocarcinomas were identified in 42, in which the number (24) of females slightly exceeded that of males. All the

TABLE 9. *Cell type and method of detection in 92 resected cases*

Cell type	Method of detection			Total
	x-Ray only	Cytology only	Dual screen	
Squamous cell ca.	11 (1)	44 (40)	4 (1)	59 (42)
Adenoca.	27 (9)	1	1	29 (9)
Small cell ca.	1 (1)			1 (1)
Large cell ca.	1			1
Adenosquamous ca.	1			1
Adenoid cystic ca.	1			1
Total	42 (11)	45 (40)	5 (1)	92 (52)

() : early lung cancer

TABLE 10. *Results of lung cancer screening according to times of screening*

Method of detection	Initial screening		Second screening*		Third screening*		Total	
	Detected cancer	Resected cancer	Detected cancer	Resected cancer	Detected cancer	Resected cancer	Detected cancer	Resected cancer
x-Ray only	41	21 (6)	24	17 (5)	6	4	71	42 (11)
Cytology only	27	24 (22)	20	17 (14)	4	4 (4)	51	45 (40)
Dual Screen	9	4 (1)	2	1			11	5 (1)
Total	77	49 (29)	46	35 (19)	10	8 (4)	133	92 (52)
% Resected		63.6%		76.1%		80%		69.2%
Number screened		169,327		121,393		66,033		356,753**
Detection rate/100,000		45		38		15		37

(), early lung cancer.

*, times of screening at the districts ; **, cumulative number of screened.

adenocarcinomas except for 1 case were detected by radiography. Small cell carcinomas (6), large cell carcinomas (10) and others (2) were also detected by radiography.

The above results indicate that radiographic and cytologic examinations play entirely different roles in the detection of lung cancers, and the above results precisely agreed with our prediction.

Resection of lung cancers by the cell type

Table 9 shows the cell types of lung cancers detected by screening and surgically resected. Of 71 cases detected by radiography only, 42 were resected. Only 11 (26%) of them were early cancers. Of 51 cases detected by sputum cytology alone, 45 (88%) were resected. Of these 45, the majority (40, 89%) were early cancers.

Lesions localized within the bronchial wall without lymph node metastasis or tumors less than 2 cm in diameter originating distally of the subregional branch and invading no further into the pleura without lymph node metastasis were defined as early cancers. These were all confirmed from the resected specimens.

As a whole, 42 (71%) of 59 squamous cell carcinomas fell into the definition of early cancer. Nine (31%) of 29 adenocarcinomas were early cancers. In total, 52 (57%) of 92 cases fell into the definition of early cancers.

Detection of lung cancers by the frequency of screening

Table 10 shows the changes in yearly detection rates of lung cancers from 1982 by the frequency of screening. The overall results in total districts indicate that the initial screening resulted in detection of 77 lung cancer patients from 169,327 participants (ratio: 45/100,000), the second screening 46 from 121,393 participants (ratio: 38/100,000) and the third screening 10 from 66,033 participants (ratio: 15/100,000), thus showing yearly decreases in detection. The rate of surgical resection of the cancers detected increased from 63.8% to 76.1% and to 80% from 1982 to 1983 to 1984. However, this does not necessarily indicate an increase in detection of early cancers with an increase in screening times. It may be because cases detected by sputum cytology included many early cancers, while lung cancers detected by radiography did not include as many peripheral early cancers as anticipated.

The total of 356,753 participants were screened from 1982. Lung cancer was detected in 133 (ratio: 37/100,000). The cancers were resected in 92 (69%). Of these, 52 (57%) were early cancers. The values obtained in the initial screening are considered to indicate the prevalence of lung cancers and this may reflect the maximum diagnostic level in the subjects examined. The values obtained in the third screening are presumed to correspond to the incidence of lung cancers.

DISCUSSION

Peripheral lung cancers are mostly adenocarcinomas. Since they are detectable with considerable efficiency by radiological examination, indirect x-rays can be performed on all participants without difficulty. Hilar lung cancers consist mostly of squamous cell carcinomas. These are directly related to a smoking habit. Since early detection of squamous cell carcinomas is impossible by radiology, sputum cytology becomes an essential means of detection. However, at present, detection of hilar lung cancers by sputum cytology is not accomplished with efficiency, and application of sputum cytology should be restricted to a limited range of patients belonging to a high-risk group.

It has been proposed that because of a low efficiency, sputum cytology be applied to patients with subjective symptoms at the time of their visit to medical organizations. As lung cancers must have already progressed by the time of such patients' visit, belated sputum cytology may be meaningless. Detection at the asymptomatic stage is important. Mass screening cannot be accomplished, unless special knowledge, sophisticated technology and steady efforts of specialist examiners together with the good-will of other members engaged in screening are ensured.

Systematic radiologic and cytologic screening for lung cancer detection has been launched in USA for the purpose of reducing the mortality from lung cancers (Taylor et al. 1981; Berlin et al. 1984). Anticipated effects on mortality and survival have not been produced as yet. No significant work has been presented at the 4th World Conference on Lung Cancer held last year in Toronto. Yearly chest x-ray examination and sputum cytology would undoubtedly contribute to early detection of squamous cell carcinomas and provide opportunities of surgical intervention. This would consequently improve the survival (Flehinger et al. 1984; Fontana et al. 1984; Frost et al. 1984).

In public opinion, screening of mass population for lung cancers is not yet encouraged due to the cost factor. However, we consider that the cost factor can be overcome if the following is put into practice. When interpreting x-ray films, every film should be examined and reexamined with the utmost care and without haste by more than one specialist. Any abnormal shadows no matter, how trifling they might seem, should be recorded and scrutinized in comparison with the x-ray films of the past 2 years. Improvements in the accuracy of radiologic evaluation and the minimizing of subsequent repeat examinations should result in the curtailment of expenditures and permit the practical application of mass screening. Double examination and interpretations by two specialists are indispensable for the evaluation of initial x-ray films, filed films and repeat x-ray films. It is also vital to record, without failure, a sketch of the abnormal shadow if detected.

On the other hand, sputum cytology requires an advanced technology. The ability of cytotechnologists and cytopathologists and their earnestness to screen-

ing sway the results of detection largely. Association of squamous epithelization and atypia in the development of squamous cell carcinoma has been little described (Saccomanno 1974). Categorization of atypia may play an important role in diagnostic establishment of lung cancers (Saito et al. 1985; Sato et al. 1985a). Especially class III cannot be strictly classified as representing malignancy but is interpreted to represent atypia that can be suspected as malignant. The class III patients in our screening program amount to 0.3-0.5% of participants who underwent sputum cytology. Repeat examinations led to the detection of lung cancer in approximately 7% of them. They were mostly early squamous cell carcinomas. All participants suspected of lung cancer by indirect radiography and sputum cytology were recalled for repeat examination. Recalling of suspected participants depends largely on the cooperation of district health nurses and efforts of local governments.

Early accurate diagnosis is not always easy. Peripheral brushing cytology is especially helpful for early accurate diagnosis (Sato et al. 1977, 1985b). When definite diagnosis fails at the initial screening, repeat examinations with more than 10 bronchoscopies occasionally resulted in localization of the lesion (Saito et al. 1984). When the possibility of lung cancer is not dismissed from the features of x-ray shadow or from the review of yearly changes, open-chest biopsy is recommended. The pathogenesis of lung cancer still remains in obscurity. The histologic patterns in progress are little known. We intend to continue data working to determine the time relation between detection and curability, definition of early cancer and intervals at which screening is to be repeated (Ikeda 1985). Screening for lung cancers depends on the effectiveness and economization. We are making preparations for establishing a system of yearly follow-up of participants screened.

The Lung Cancer Screening Project in USA appears to have been scrupulously planned from an epidemiological viewpoint. However, the number of cytologically detected patients was not high, contrary to our expectation. Of 71 lung cancers detected by radiography alone, 42 underwent resection, of which only 11 (26%) were early cancers. Of 51 detected by sputum cytology alone, 45 (88%) underwent resection, of which 40 (89%) were early cancers.

We consider that goal of early detection of curable lung cancers has been attained. We also consider that a final goal, diminution of mortality from lung cancer, is not an empty dream to attain.

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