Acta Med. Okayama, 2006
Vol. 60, No. 3, pp. 173–179


Acta Medica Okayama
http://www.lib.okayama-u.ac.jp/www/acta/

*Original Article*

# Recent Improvement in Lung Cancer Screening: A Comparison of the Results Carried Out in Two Different Time Periods

**Takuji Kitajima[a], Kenji Nishii[b]*, Hiroshi Ueoka[a], Takuo Shibayama[c], Kenichi Gemba[d], Tsuyoshi Kodani[b], Katsuyuki Kiura[a], Masahiro Tabata[a], Katsuyuki Hotta[a], Mitsune Tanimoto[a], and Tomotaka Sobue[e]**

*[a]Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, [b]Department of Respiratory Medicine, Okayama Institute of Health and Prevention, Okayama 700–0952, Japan, [c]Department of Internal Medicine, National Sanatorium Minami-Okayama Hospital, Okayama 701–0304, Japan, [d]Respiratory Disease Center for Workers, Okayama Rousai Hospital, Okayama 702–8055, Japan, and [e]Cancer Information and Epidemiology Division, National Cancer Center Research Institute, Tsukiji, Chuo-ku, Tokyo 104–0045, Japan*

**To evaluate recent improvements in lung cancer screening, we compared the results of recently conducted lung cancer screening with those of a previous screening. This study compared the survival of lung cancer patients detected by lung cancer screening conducted between 1976 and 1984 (early period) with that conducted between 1989 and 1997 (late period). Two hundred seventy-six patients with lung cancer were detected in the early period and 541 patients with lung cancer were detected in the late period. The median survival time (late: 49.8 vs. early: 27.8 months) and the 5-year survival rate (late: 47.8 vs. early: 34.8%) of the patients with lung cancer detected in the late period were significantly better than those in the early period ($p = 0.0054$). Among patients undergoing resection, the proportion of pathological stage I patients in the late period was significantly higher than that in the early period (late: 60.8 vs. early: 54.9%, $p = 0.005$). Multivariate analysis showed that the screening time period was a significant prognostic factor (hazard ratio = 0.685, 95% confidence interval: 0.563–0.832, $p = 0.0002$). These results were consistent with the findings of case-control studies of lung cancer screening programs in the late period recently conducted in Japan, which also showed a greater efficacy for screening than for previous case-control studies in the early period.**

**Key words**: lung cancer, screening, survival, lung cancer mortality

Currently, lung cancer is the leading cause of cancer-related death in Japan, with 50,871 patients dying of lung cancer in 1998 [1]. In an attempt to reduce lung cancer mortality, lung cancer screening with chest x-ray and sputum cytology utilizing the screening system developed for pulmonary tuberculosis were performed in Japan until 1986. Since 1987, the Japanese government, on the basis of the Health and Medical Services Law for the Aged, has supported lung cancer screening.

Received September 8, 2005; accepted December 27, 2005.
*Corresponding author. Phone: +81–86–241–0880; Fax: +81–86–241–9365
E-mail: nkenji@lime.ocn.ne.jp (K. Nishii)

However, to date, the effectiveness of lung cancer screening has not been established. In the USA, the effectiveness of lung cancer screening was assessed in randomized trials sponsored by the National Cancer Institute (NCI) conducted at Johns Hopkins University [2], Memorial Sloan-Kettering Cancer Center [3], and the Mayo Clinic [4] in the 1970s. Although these trials demonstrated that the resectability and survival of lung cancer patients in the screening group were superior compared with those in the control group, no reduction in overall lung cancer mortality was shown. These results were thought to be due to lead-time bias or over-diagnosis bias [5, 6]. Based on these findings, the U.S. Preventive Services Task Force declared that routine screening for lung cancer with chest radiography or sputum cytology in asymptomatic persons was not recommended (U.S. Preventive Services Task Force home page 〈http: //www.ahcpr.gov/clinic/uspstf/uspslung.htm〉, accessed on Oct 17, 2005).

On the other hand, Sobue *et al.* in Japan evaluated the effectiveness of the annual chest x-ray system developed for pulmonary tuberculosis screening conducted between 1977 and 1987. Using a case-control design, they showed a reduction of lung cancer mortality by a maximum of 28% (odds ratio: 0.72, 95% confidence interval: 0.50–1.03). Their data included part of the screening results conducted in the Okayama prefecture. However, their results were not statistically significant ($p=0.07$) [7]. In 1998, 4 case-control studies — including our study [8], supported by the Ministry of Health and Welfare — were planned in Japan to evaluate the effectiveness of the new lung cancer screening program supported by the government under the Health and Medical Services Law for the Aged [8–11]. Our study evaluated 412 patients who died of lung cancer between 1991 and 1996 in the Okayama prefecture and showed that lung cancer screening significantly reduced lung cancer mortality by 41% (smoking-adjusted odds ratio = 0.59; 95% confidence interval: 0.46–0.74; $p=0.0001$) [8]. Furthermore, 2 other studies also showed a significant reduction of lung cancer mortality as a result of screening [9, 10]. In order to elucidate why the recent lung cancer screening reduced lung cancer mortality while previous studies had shown negative results, we designed a comparison of the data gathered from the recent lung cancer screening with the older screening data.

## Materials and Methods

This study compared the results of lung cancer screening conducted between 1976 and 1984 (early period), which were used in the Sobue study [7], with those gathered between 1989 and 1997 (late period), which were used in the Nishii study [8]. The study area of the 2 cohorts was the same (Okayama prefecture). In the early period, the Tuberculosis Control Law required all citizens aged 16 or over to have a chest x-ray annually. The lung cancer screening program, which was conducted in the late period, was performed on individuals aged 40 or over as legislated by the Health and Medical Services Law for the Aged. Only the national health insurance holders or family members of the employment-related health insurance holders underwent screening in this program, since the Employment-related health insurance holders were assigned to be screened by their companies using a different system. As an annual chest x-ray examination, $70\times70$ mm miniature photofluorography with a tube voltage of 100 kV was used in the early period and a $100\times100$ mm miniature photofluorography with tube voltage of 140 kV was used in the late period. The smoking habits of all participants were recorded. Sputum cytology with Saccomanno's 3-day pooled method was performed for individuals in the high-risk group, which included individuals aged 50 or over with a smoking index (average number of cigarettes smoked per day multiplied by the number of years smoked) of at least 600. For the individuals who were suspected to have lung cancer by chest x-ray or sputum cytology, further examinations were performed as soon as possible to confirm the diagnosis.

Data on diagnosis, clinical stage, therapy, and survival were obtained from hospital records and/or data in the Okayama Cancer Registry. Histologic types were classified according to the World Health Organization histologic classification [12]. The clinical stage of lung cancer was determined on the basis of the American Joint Committee on Cancer classifications [13].

Categorical variables were compared using the $X^2$ test. Survival rates were calculated by the Kaplan-

Meier method. We assessed the prognostic significance of lung cancer screening by univariate analysis using a log-rank test and multivariate analysis using Cox's proportional hazards model. The variables analyzed in this study were age ($\geq 70$ years vs. $< 70$ years), sex, histology (adenocarcinoma vs. non-adenocarcinoma), clinical stage (I vs. II, III, IV), and era (1976–1984 vs. 1989–1997), and hazard ratios and their 95% confidence intervals were estimated. Statistical analysis was performed using SPSS Software (SPSS Inc, Chicago, IL, USA). A $p$ value of 0.05 was considered statistically significant.

## Results

The characteristics of the patients are shown in Table 1. Two hundred seventy-six patients with lung cancer were identified in the early period and 541 patients were identified in the late period. Patients identified in the early period were younger on average than those in the late period, which might be due to the difference in the age limitation of the accrued subjects in each cohort. Similarly, the proportion of adenocarcinoma or clinical stage I was slightly lower and that of squamous cell carcinoma or stage IV was higher in the early period. However, these differences were not statistically significant.

Survival curves according to screening period are shown in Fig. 1. Median survival time (MST) and 5-year survival rate (5-yr) in the late period were 49.8 months and 47.8%, respectively, which were significantly better than those (MST: 27.8 months and 5-yr: 34.8%) in the early period ($p = 0.0054$). Regardless of clinical stage, survival rates in the late period were better than those in the early period. However, a statistically significant difference was obtained only in patients with stage IV disease (Table 2, $p = 0.0423$). Survival curves according to treatment modality are shown in Fig. 2. Significant improvement in the late period was obtained in patients receiving chemotherapy (MST: 13.2 months late vs. 10.2 months early, $p = 0.0035$), but no difference was shown in patients undergoing surgical resection (MST: not calculated, 5-year survival rate: 51.4% late vs. 65.0% early, $p = 0.1403$), radiotherapy (MST: 15.2 months late vs. 16.0 months early, $p = 0.6452$) or supportive care alone (MST: 13.7 months late vs. 16.0 months early, $p = 0.4293$).

One hundred seventy-three (62.7%) of 276 patients underwent surgical resection in the early period compared to 378 (69.9%) of 541 patients in the late period. The resection rate in the late period was significantly higher than that in the early period ($p = 0.038$). There was no significant difference in the resection rate based on histology. Among patients undergoing resection, the proportion of the pathological stage I patients in the late period (230/541: 60.8%) was significantly higher than that in the early period (95/173: 54.9%, $p = 0.005$).

**Table 1** Characteristics of patients with lung cancer detected by population-based screening

| | | Early period 1976–1984 | Late period 1989–1997 |
|---|---|---|---|
| No. evaluated | | 276 | 541 |
| Median age (range) | | 64 (34–81) | 69 (35–91) |
| Sex: | male | 185 (67%) | 371 (69%) |
| | female | 91 | 170 |
| Histology: | | | |
| | adenocarcinoma | 155 (56%) | 327 (60%) |
| | squamous cell ca. | 86 (31%) | 141 (26%) |
| | small cell ca. | 28 (10%) | 53 (10%) |
| | others | 7 ( 3%) | 20 ( 4%) |
| Stage: | I | 156 (57%) | 338 (62%) |
| | II | 45 (16%) | 43 ( 8%) |
| | IIIA | 25 ( 9%) | 84 (16%) |
| | IIIB | 12 ( 4%) | 29 ( 5%) |
| | IV | 38 (14%) | 47 ( 9%) |

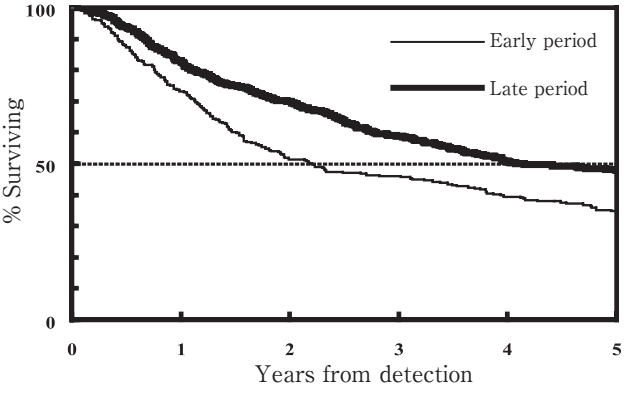


**Fig. 1** Survival curves of lung cancer patients according to era detected by lung cancer screening (276 patients in the early period vs. 541 patients in the late period). Kaplan-Meier method.

However, the 5-year survival rate in pathological stage I patients did not differ between the 2 periods (77.4% vs. 78.1%, $p=0.3532$, Fig. 3).

We also investigated the effect of time difference of screening on survival by uni- and multi-variate analyses. On univariate analysis, the late era as well as younger age (<70 years old), female gender, adenocarcinoma histology, and clinical stage I were significantly associated with better prognosis (Table 3). Multivariate analysis using Cox's proportional hazard model also showed that the clinical stage was the most significant variable and that age was the second most significant. As well, the screening time period was also confirmed as a significant prognostic factor (hazard ratio=0.685, 95% confidence interval: 0.563–0.832, $p=0.0002$; Table 4).

**Table 2** Survival of patients with lung cancer according to clinical stage

| Stage | Early period (1976 – 1984) | | Late period (1989 – 1997) | | *p*-value |
|---|---|---|---|---|---|
| | No. of patients | MST (mo) | No. of patients | MST (mo) | |
| I | 156 (57%) | not calculated | 338 (63%) | not calculated | 0.3532 |
| II | 45 (16%) | 17.3 | 43 (8%) | 29.6 | 0.1277 |
| IIIA | 25 (9%) | 14.8 | 84 (16%) | 21.7 | 0.2286 |
| IIIB | 12 (4%) | 10.3 | 29 (5%) | 13.8 | 0.1149 |
| IV | 38 (14%) | 5.8 | 47 (9%) | 8.6 | 0.0423 |

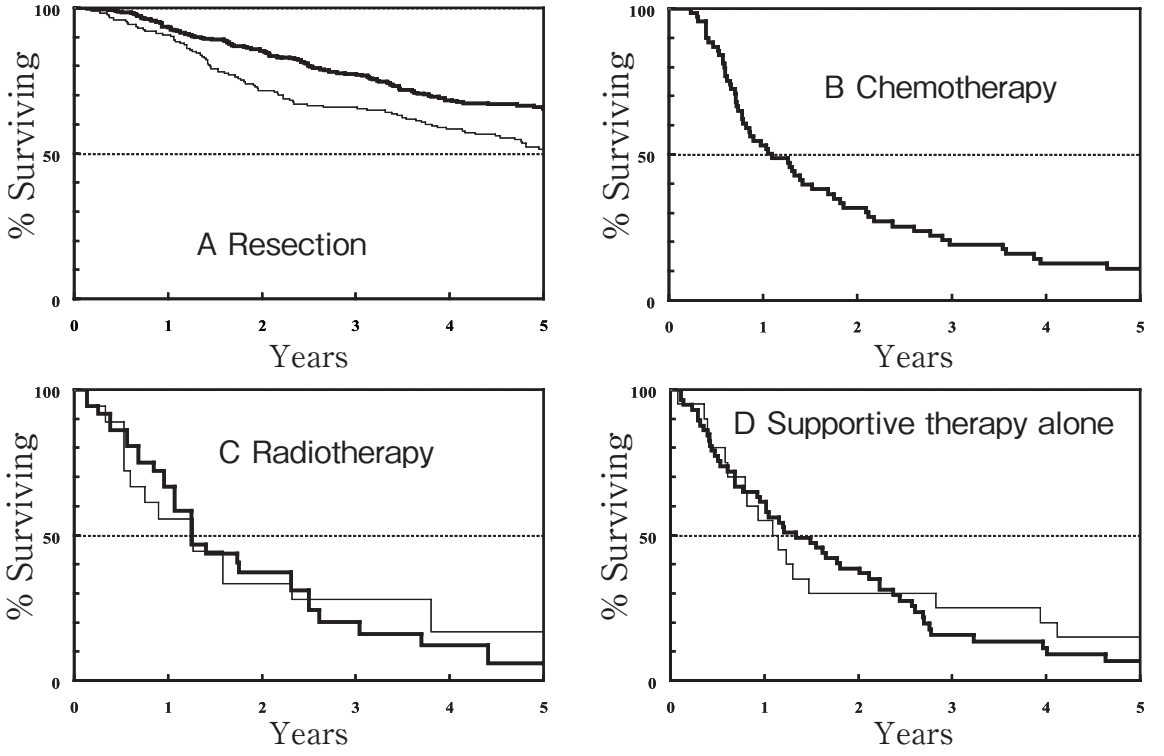


**Fig. 2** Survival curves of lung cancer patients according to era (early period vs. late period). Kaplan-Meier Method: thick line, late period; thin line, early period.
**A**, Survival curves according to resection (173 patients vs. 378 patients); **B**, Survival curves according to chemotherapy (65 patients vs. 70 patients); **C**, Survival curves according to radiotherapy (18 patients vs. 36 patients); **D**, Survival curves according to supportive therapy alone (20 patients vs. 57 patients).

Table 3 Univariate analysis

| Variables | No. of patients | Median survival time (months) | *p*-value |
|---|---|---|---|
| Era | | | |
| 1976–1984 | 276 | 27.8 | 0.0054 |
| 1989–1997 | 541 | 49.8 | |
| Age: | | | |
| less than 70 year-old | 467 | – | < 0.0001 |
| 70 year-old or older | 350 | 29.3 | |
| Sex: | | | |
| male | 556 | 34.8 | < 0.0001 |
| female | 261 | – | |
| Histology: | | | |
| adenocarcinoma | 482 | 60.0 | < 0.0001 |
| non-adenocarcinoma | 335 | 28.9 | |
| Clinical stage: | | | |
| stage I | 494 | – | < 0.0001 |
| stage II–IV | 323 | 12.4 | |

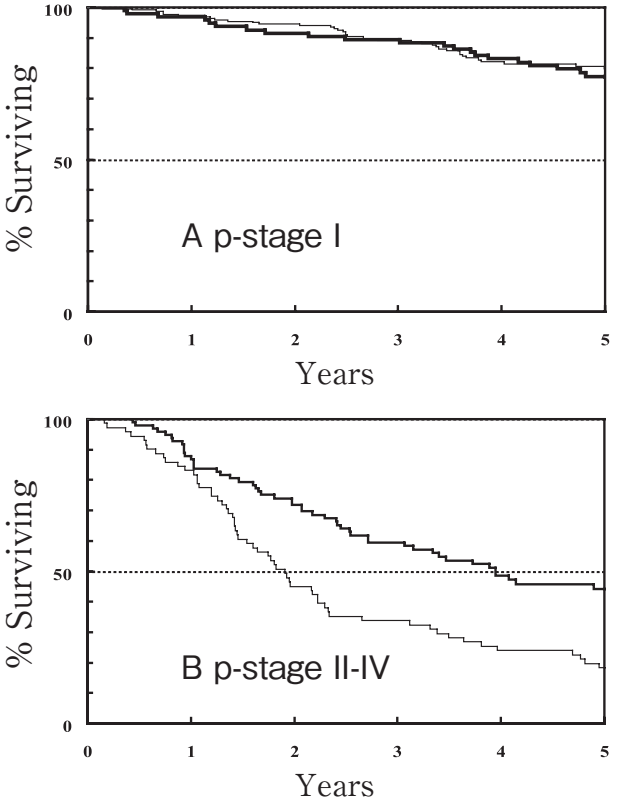


Fig. 3 Survival curves of lung cancer patients according to pathological stage (early period vs. late period). Kaplan-Meier method; thick line, late period; thin line, early period.
**A**, Survival curves of patients with p-stage I disease (95 patients vs. 230 patients); **B**, Survival curves of patients with p-stage II–IV disease (71 patients vs. 99 patients).

## Discussion

In order to confirm the recent improvement in lung cancer screening, we designed the present study and found that the survival of patients detected in the late period was significantly better than that in the early period, though statistically significant differences between time periods in clinical characteristics, such as histology and stage, were not observed. There are several possible explanations for the statistically significant survival benefit obtained in the late period.

First, more patients with an earlier stage of lung cancer, even though technically within the same stage, may have been detected in the late period. The detection rates of lung cancer did not differ between the 2 groups: 0.0470% of participants screened between 1976 and 1984 and 0.0491% of those screened between 1989 and 1997. However, the resection rate in the late period was higher than that in the early period (69.9% late vs. 62.7% early, $p = 0.038$). By using a larger film ($100 \times 100$ mm miniature photofluorography) and higher tube voltage (140 kV), more information could be obtained on chest x-ray examination compared with the previously used method ($70 \times 70$ mm miniature photofluorography with a tube voltage of 100 kV). This may have enabled the detection of earlier lung cancer. Furthermore, better training of doctors performing the screening and prompt examination of suspected cases became possible due to the Health and Medical Services Law for the Aged; and this also may have influenced the results.

Second, the advancement of lung cancer treatment modalities may have improved the results of screening in recent years. In the present study, the survival of patients with stage II–IV disease in the late period was significantly better than that in the early period, yet no improvement was shown for patients with stage I disease (Fig. 3). Advancements in chemotherapy may have affected these results. This would appear to be confirmed by the fact that survival improvement was obtained only in patients

Table 4 Multivariate analysis

| Prognostic factor | Hazard ratio | 95%CI* | *p*-value |
|---|---|---|---|
| Era (1989–1997 vs. 1976–1984) | 0.69 | 0.563–0.832 | 0.0002 |
| Clinical stage (stage II–IV vs. I) | 3.99 | 3.288–4.841 | < 0.0001 |
| Age ( ≧ 70 vs. < 70 yo) | 1.61 | 1.333–1.951 | < 0.0001 |
| Sex (male vs. female) | 1.31 | 1.050–1.623 | 0.0343 |
| Histology (non-adenoca. vs. adenoca.) | 1.06 | 0.870–1.298 | 0.5527 |

*95%CI = 95% confidence interval.

receiving chemotherapy (Fig. 2). However, the majority of the patients detected by mass screening might have had non-small cell lung cancer, and there were no remarkable advancements in systemic chemotherapy for such cases during the period between the former and latter screening programs. Thus, it appears to be unrealistic to assume that advancements in chemotherapy could be the main reason for the improvement in survival seen in the late period.

Third, a recent increase in peripheral lung adenocarcinoma, which can be detected by chest x-ray without difficulty and generally has a good prognosis, may have affected the results. In the present study, the proportion of adenocarcinoma was shown, in fact, to have increased in the late period.

There are several limitations in this study. The current study may have a lead-time bias; however, although the proportion of pathological stage I patients among those undergoing resection was significantly higher in the late period, the survival of stage I patients did not differ between the 2 time periods. This suggests that its bias might be minimal. As another problem, we did not assess cost-effectiveness of the recent screening program; the survival advantage we demonstrated was the principal goal of the study. Based on these limitations, the results we obtained should be cautiously interpreted.

In conclusion, we found that (i) the survival of patients with lung cancer detected in the late period was significantly better than that of those in the early period; (ii) among the patients undergoing resection, the proportion of pathological stage I patients in the late period was significantly higher than that in the early period; and (iii) multivariate analysis showed that the screening time period was a significant prognostic factor. These observations indicate a greater efficacy for the recent screening program than for case-control studies in the early period. Furthermore, a reanalysis of the Mayo Lung Project data, which showed that the survival in the screened population was superior to that in the unscreened population [14], has been encouraging. Therefore, we have to reconsider the effectiveness of lung cancer screening and to continue studying how to improve its sensitivity and specificity.

Acknowledgements. We would like to thank Ms. Masakage and Ms. Tanaka for collecting the data for this study.

## References

1. Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare. in Vital Statistics 1998 Japan, Health and Welfare Statistics Association, Tokyo (2000).
2. Melamed MR and Flehinger BJ. Detection of lung cancer: Highlights of the Memorial Sloan-Kettering Study in New York City. Schweitz Med Wochenschr (1987) 117: 1457–1463.
3. Tockman MS: Survival and mortality from lung cancer in screened population: The Johns Hopkins Study. Chest (1986) 89: 324–325.
4. Fontana RS, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR, Bernatz PE, Payne WS, Pairolero PC and Bergstralh EJ: Screening for lung cancer, a critique of the Mayo Lung Project. Cancer (1991) 67: 1155–1164.
5. Patz EF Jr, Goodman PC and Bepler G: Screening for lung cancer. N Engl J Med (2000) 343: 1627–1633.
6. Marcus PM, Bergstralh EJ, Fagerstrom RM, Williams DE, Fontana R, Taylor WF and Prorok PC: Lung cancer mortality in the Mayo Lung Project: Impact of extended follow-up. J Natl Cancer Inst (2000) 92: 1308–1316.
7. Sobue T, Suzuki T and Naruke T: A case-control study for evaluating lung-cancer screening in Japan. Japanese Lung-Cancer-Screening Research Group. Int J Cancer (1992) 50: 230–237.
8. Nishii K, Ueoka H, Kiura K, Kodani T, Tabata M, Shibayama T, Gemba K, Kitajima T, Hiraki A, Kawaraya M, Nakayama T and Harada M: A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer (2001) 34: 325–332.
9. Sagawa M, Tsubono Y, Saito Y, Sato M, Tsuji I, Takahashi S, Usuda K, Tanita T, Kondo T and Fujimura S: A case-control study for evaluating the efficacy of mass screening program for lung cancer in Miyagi Prefecture, Japan. Cancer (2001) 92: 588–594.
10. Tsukada H, Kurita Y, Yokoyama A, Wakai S, Nakayama T, Sagawa M and Misawa H: An evaluation of screening for lung

cancer in Niigata Prefecture, Japan: a population-based case-control study. Br J Cancer (2001) 85: 1326–1331.
11. Nakayama T, Baba T, Suzuki T, Sagawa M and Kaneko M: An evaluation of chest X-ray screening for lung cancer in Gunma Prefecture, Japan: a population-based case-control study. Eur J Cancer (2002) 38: 1380–1387.
12. WHO: Histological typing of lung tumors, 2nd Ed, Geneva (1981).
13. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest (1997) 111: 1710–1717.
14. Strauss GM: The Mayo Lung Cohort: A regression analysis focusing on lung cancer incidence and mortality. J Clin Oncol (2002) 20: 1973–1983.