The Natural History of Radiographically Occult Bronchogenic Squamous Cell Carcinoma*

A Retrospective Study of Overdiagnosis Bias

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Objective: An overdiagnosis bias occurs with the diagnosis of a disease that does not produce signs or symptoms before the patient dies from other causes. We sought to determine whether overdiagnosis bias is a factor when screening for squamous cell carcinoma of the lung.

Design: Retrospective study of the Miyagi Population-Based Lung Cancer Screening Registry for high-risk patients who were seen between January 1, 1982 (when sputum cytology tests were added for men with long smoking histories) and December 31, 1996.

Setting: Miyagi Prefecture, Japan.

Patients: A total of 251 patients (all men) who had sputum cytology test results that were positive for squamous cell carcinoma but had normal radiograph findings, 44 of whom declined cancer treatment (mean age, 70 years) and 207 of whom were treated with resection within 12 weeks of diagnosis (mean age, 65.5 year).

End Points: Five-year and 10-year survival rates from primary lung cancer in both groups as of August 15, 2001.

Results: Among the 44 untreated patients, 15 (34%) remained asymptomatic. The survival rate due to primary lung cancer death in the untreated group was 53.2% at 5 years and 33.5% at 10 years. The survival rate among treated patients was 96.7% at 5 years and 94.9% at 10 years. Of the 125 treated patients who died, 14 (11.2%) died from primary lung cancer.

Conclusion: Given that the two thirds of the untreated patients with squamous cell carcinoma of the bronchus died from lung cancer within 10 years, overdiagnosis bias does not appear to be a factor in screening for this disease. Thus, we recommend that patients with radiographically occult squamous cell carcinoma of the bronchus undergo tumor treatment after localization.

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Key words: early detection; lead-time bias; lung cancer; mass screening; overdiagnosis bias; sputum cytology; squamous cell carcinoma; tumor localization

Abbreviation: CI = confidence interval

The concept of overdiagnosis, as formulated after the Mayo Lung Project,1–6 is based on the fact that many patients with slow-growing cancers will likely die of other causes before the cancer produces clinical signs and symptoms. In such cancers, screening programs for the early diagnosis of cancer will produce an overdiagnosis bias by diagnosing patients with a cancer that may not need to be treated.

Screening for lung cancer has been thought to be
ineffective, and overdiagnosis bias has been used to explain the disappointing results of mass screening programs. However, in the late 1990s, the Mayo Lung Project was reevaluated, and some authors have suggested the possible usefulness of chest radiography for lung cancer screening. Knowing the natural course of a disease in untreated patients can be helpful in determining the presence of overdiagnosis bias. Sobue et al reported the course of nonsurgically treated, clinical stage I lung cancer detected by radiography. Including their report, most studies have dealt with adenocarcinoma diagnosed from an abnormal shadow on a radiograph. To our knowledge, however, the natural course of radiographically negative squamous cell carcinoma of the lung has not been described. Patients who have cytologic evidence of lung cancer but have normal chest radiographs are thought to be in the early stages of cancer. The introduction of autofluorescence bronchoscopy has made it easy to detect many intraepithelial lesions. However, it is not known whether these lesions should be treated or not. Clarifying the natural history of this type of lung cancer could help to determine whether a latent or nonprogressive form of squamous cell carcinoma exists and, in turn, whether this cancer is subject to overdiagnosis bias.

In the United States, lung cancer screening tests are generally administered only to persons with good cardiopulmonary function who can undergo surgical treatment. Japan, however, has a 50-year history of screening for tuberculosis with chest radiography. Everyone is screened because some people remain worried about tuberculosis. As a result, some people with poor cardiopulmonary function in whom cancer is detected may decline cancer treatment. Others may mistake sputum cytology, which became part of the screening program in 1982, as a screening test for tuberculosis and thus may also decline treatment for lung cancer if it is diagnosed. We took advantage of this unique situation, in which patients with cytologic evidence of squamous cell carcinoma and normal chest radiograph findings remain untreated, to study the natural history of squamous cell carcinoma. We herein report the results of a retrospective study of a cancer screening registry in which we compared the survival of cancer patients with cytologic evidence of squamous cell carcinoma and normal chest radiograph findings, who did and did not undergo tumor resection.

**Patients and Methods**

We reviewed the registry of the Miyagi Population-Based Lung Cancer Screening Program, which is a database of people from Miyagi Prefecture who were screened with radiography, originally for tuberculosis and later for lung cancer. In 1982, the registry added sputum cytology as a new screening method for the early detection of lung cancer. Men with a Brinkman index of ≥600 were candidates for screening.

All patients with abnormal sputum cytology test results were examined at the Department of Thoracic Surgery, Tohoku University Hospital, where they underwent CT scans of the chest and bronchoscopy. When patients had abnormal radiographic findings, they were referred to other hospitals.

Records dated between January 1, 1982, and December 31, 1996, were studied to identify patients in whom sputum cytology test results were positive for squamous cell carcinoma of the lung and in whom the findings of miniature (ie, 100 mm × 100 mm) posteroanterior chest radiographs were normal. These patients constituted two groups, namely, those who chose not to receive treatment for cancer and those who underwent tumor resection (Table 1). Patients receiving radiotherapy or photodynamic therapy were excluded.

Willing patients in the untreated group underwent a chest radiograph and sputum cytology test every 4 months, chest CT scans every 6 months, and bronchoscopic examinations every 12 months. The cause of death for patients who died before August 15, 2001, also was obtained from the registry. Death from primary lung cancer was defined as a tumor in the lung that was accompanied by clinical complications, such as obstructive pneumonia, hemoptysis, or brain metastasis. When the registry did not list the patient’s cause of death, we used the cause of death identified by the patient’s personal physician. The end points of this study were the 5-year and 10-year survival rates from primary lung cancer in both groups.

**Statistical Analysis**

Kaplan-Meier curves were plotted for both treated patients (ie, those who underwent resection) and untreated patients using a statistical software package (StatView; SAS Institute; Cary, NC).

**Results**

We identified 251 patients (all men) with positive sputum cytology test results and normal radiograph findings (Table 1). Of these patients, 44 did not receive treatment for cancer (ie, untreated patients). The mean (±SD) age was 70 ± 8.2 years (age range, 51–81 years).

**Table 1—Background of Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Natural Course Cases (n = 44)</th>
<th>Resected Cases (n = 207)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>All male</td>
<td>All male</td>
</tr>
<tr>
<td>Age</td>
<td>Mean/SD 70/8.2</td>
<td>65.5/6.5</td>
</tr>
<tr>
<td>Minimum—maximum</td>
<td>53—56</td>
<td>51—81</td>
</tr>
<tr>
<td>Brinkman index†</td>
<td>Mean/SD 1.065/381</td>
<td>1.053/442</td>
</tr>
<tr>
<td>Minimum—maximum</td>
<td>500—2,400</td>
<td>400—3,420</td>
</tr>
</tbody>
</table>

*Two patients who died within 30 days after operation were excluded.
†Brinkman index: (No. of cigarettes per day) × (No. of years subject has smoked).
‡In 10 patients, we could not obtain information about the smoking history.
In this group, 27 patients had tumors that were localized by bronchoscopic examination, but they nevertheless declined treatment, 13 patients declined bronchoscopic examinations, and 4 patients had disease that could not be localized, even after intensive examinations, including bronchoscopy, CT scans of the chest, and inspections by otorhinolaryngologists. These last 17 patients were eventually confirmed as having lung cancer at a mean of 49 months after the initial examination (range, 4.6 to 160 months).

Although the smoking histories of 10 untreated patients were not available, the 34 remaining patients each had a history of smoking. The mean Brinkman index (i.e., the number of cigarettes smoked per day times the number of years of smoking) was 1,065 (range, 500 to 2,400).

We also identified 207 patients who underwent pulmonary resection shortly after learning the results of the sputum cytology test (treated patients). The mean age was 65.5 years (SD, 6.5 years) [age range, 51 to 81 years]. The mean Brinkman index was 1,053 (range, 400 to 3,420).

The overall survival rates of the 44 untreated patients were 53.2% at 5 years and 33.5% at 10 years (Fig 1). Among the 44 untreated patients, 15 (34%) remained asymptomatic. Nine of the 15, however, died due to the following conditions: cardiovascular disease (4 patients); extrapulmonary malignancy (2 patients); emphysema (1 patient); and unknown causes (2 patients).

The survival rates based on death from primary lung cancer in the 207 treated patients were 96.7% at 5 years and 94.9% at 10 years (Fig 1). None of these patients had abnormal radiographic findings at the time of treatment.

Of the 207 surgically treated patients, 125 (60%) died within 10 years (from primary lung cancer, 14 [11%]; from metachronous secondary lung cancer, 28 [22%]) [Table 2]. Thus, among treated patients who died, the rate of lung cancer death, including the first primary and metachronous second primary lung cancer, was 33.6% (42 of 125 patients).

We also analyzed data from 19 additional patients with radiographically occult lung cancer, identified as described, who initially declined treatment but who eventually sought treatment for cancer. When cancer cells were present in the sputum anytime during the follow-up period, or when chest radiographs showed abnormalities, we recommended bronchoscopic examination to the patients. At the time of treatment, all 19 patients had lung cancer, as diagnosed bronchoscopically, but chest radiograph findings were still normal in 10 patients and abnormal in 9 patients.

In the 10 patients with normal radiograph findings, there were no lung cancer deaths. However, patients who had abnormal shadows at the time of treatment had worse prognoses (Fig 2).

**DISCUSSION**

Overdiagnosis bias is often discussed in the field of mass cancer screening. The concept is easily understood, and many authors have used it when discussing their data. However, this bias is difficult to evaluate. One common approach is to analyze autopsy data to determine retrospectively the incidence of undiagnosed cancer. However, this method yields only the prevalence of cancer at the time of autopsy and does not include much information concerning the development of the disease. Drlicek and
Bodenteich\textsuperscript{27} examined a large number of autopsy reports from three hospitals and reported an overall incidence of undiagnosed lung cancer of 7.8\% (67 of 859 patients). He also reported the incidence of clinically undiagnosed lung cancer for each of the three hospitals. The incidence of undiagnosed cancer in the hospital having a pulmonary department was 3.4\%, which was the lowest among the three hospitals.

Another way of evaluating overdiagnosis bias is to observe patients who have received a diagnosis of cancer but who have not received treatment. Ethical issues do not allow a prospective study of such patients. Since 1982, we have been conducting lung cancer screening tests with both miniature chest radiographs and sputum cytology among high-risk individuals whose Brinkman index is $>600$. Between 1982 and 1996, we detected 282 cases of bronchogenic squamous cell carcinoma with sputum cytology tests in patients with normal chest radiograph findings, 251 of whom had undergone resection or had declined treatment. (The latter 251 patients were included in the present analysis. The remaining 31 excluded patients consisted of 15 patients who received radiotherapy and 16 patients who were treated with photodynamic therapy.) Although almost all the patients were asymptomatic, most chose to undergo treatment. Among them, however, were 44 patients reported here who declined further examination or treatment and 19 patients who eventually sought treatment when the diagnosis was confirmed. We analyzed the natural course of the disease in these patients because we could observe, retrospectively, the biological behavior of the cancer.

We also analyzed the survival curves of the occult lung cancer patients who underwent complete resection. A few of these patients died from a recurrence of resected cancer, although their resected tumors were small. This result indicates that some of these patients had an extremely high malignant potential, despite the cancer being at an early stage at the time of surgery. It also suggests that overdiagnosis bias is not applicable in all cases of radiographically occult bronchogenic squamous cell carcinoma.

All the untreated patients had cancer cells in their sputum, but all had normal chest radiograph findings. Two thirds of the patients died from lung cancer within 10 years. This finding indicates that overdiagnosis bias is not a major factor in such patients. We speculate that a long lead-time bias is a key factor in understanding the natural course as well as the clinical course in this group. In cases in which tumors could not be localized but showed positive cytology results, some tumors in the oropharyngeal region were detected during the follow-up period. In this study, however, we focused on the natural course of radiographically occult bronchogenic squamous cell carcinoma. Thus, the data of patients with tumors in the oropharyngeal region are not included in this report. Similarly, regarding the treatment group, we chose patients who had undergone pulmonary resection from among those who received various kinds of treatment, because pulmonary resection is believed to be the most curative.

To our knowledge, no one has described the natural course of patients with radiographically occult, bronchogenic squamous cell carcinoma. Sobue et al\textsuperscript{18} described the course of stage I lung cancer. The 5-year survival rate was 14.3\% for the screening-detected group and 3.7\% for the symptom-detected group.\textsuperscript{18} Because the patients of Sobue et al\textsuperscript{18} had abnormal shadows on their radiographs, the difference between the 5-year survival rate of their patients and ours is also understandable in terms of lead-time bias. Nou,\textsuperscript{19} reporting on the natural course of bronchial carcinoma, found a 5-year survival rate of 7.5\% in cases of squamous cell carcinoma detected by radiography. He did not document cancer stage distributions, however.

Motohiro et al\textsuperscript{20} examined the prognosis of nonsurgically treated clinical stage I lung cancer patients and reported a 5-year survival rate of about 20\%. Interestingly, he also found that the survival rate continued to decrease after 5 years. Although his cases were detected by radiography, we believe they support our results. In an early report of the Mayo Lung Project, Woolner et al\textsuperscript{4} described a case in which positive sputum findings preceded the development of a radiographic abnormality.

In addition to the Mayo Lung Project, two other famous randomized trials, the Johns Hopkins Study\textsuperscript{28,29} and the Memorial Sloan-Kettering study\textsuperscript{30,31} also have addressed this issue. Based on the
results of the Sloan-Kettering study, Melamed et al. concluded that the squamous cell carcinomas detected by cytologic examination alone are very slow growing and tend to remain localized until detected by radiography. This conclusion may be based on the fact that survival and mortality rates in their study were the same between the screened and control groups. Thus, we tried to observe the treatment results of the patients who received treatment later. The 9 patients who had abnormal radiographic shadows at the time of their delayed treatment had a worse prognosis than did the 10 patients with normal radiographic screening.

Finally, three randomized controlled trials in the United States in the late 1970s and early 1980s reported that screening with sputum cytology did not reduce deaths from lung cancer. The Johns Hopkins Study and the Memorial Sloan-Kettering study examined the effectiveness of sputum cytology screening in combination with radiographic screening compared with that of radiographic screening alone. There were 2.7 lung cancer deaths per person-year in both the screened and the control group in the Memorial Sloan-Kettering study, and 3.4 per person-year in the screened group and 3.8 per person-year in the control group in the Johns Hopkins Study.

Sagawa et al., however, reported on the efficacy of lung cancer screening conducted in the 1990s. He reported four case-control studies in Japan, three of which revealed statistically significant reductions in lung cancer deaths among screened patients. The odds ratios in each study were 0.54 (95% confidence interval [CI], 0.41 to 0.73) in Miyagi Prefecture, 0.40 (95% CI, 0.27 to 0.59) in Niigata Prefecture, 0.59 (95% CI, 0.46 to 0.74) in Okayama Prefecture, and 0.68 (95% CI, 0.44 to 1.05) in Gunma Prefecture. In the three studies showing significant reductions, high-risk persons (ie, smokers) were screened with annual chest radiographs and sputum cytology tests, and nonsmokers were screened with an annual chest radiograph. In the one prefecture in which screening did not yield a significant reduction in lung cancer deaths, only annual radiographs were used.

**Limitations of the Study**

Our study was retrospective and nonrandomized, so the groups were not necessarily equivalent at baseline. For example, the age distributions were slightly different between the two groups. Patients who underwent resection likely had a will to survive and a strong interest in their health, whereas those who declined treatment may not have. Our study cannot exclude such biases. Our study nevertheless offers some important information on the natural course of radiographically occult squamous cell carcinoma of the bronchus.

**Conclusion**

In conclusion, although some investigators believe that cancer patients with normal radiograph findings have slow-growing tumors, two thirds of the patients with such tumors in our study died from primary lung cancer within 10 years. This result suggests that overdiagnosis bias is not a factor in the course of squamous cell carcinoma of the bronchus in patients with normal chest radiograph findings. We recommend that these patients be treated after the tumor is localized.

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**References**


