Lung Cancer in Women*
Sex-Associated Differences in Survival of Patients Undergoing Resection for Lung Cancer

Hiroya Minami, MD; Masahiro Yoshimura, MD; Yoshifumi Miyamoto, MD; Hidehito Matsuoka, MD; and Noriaki Tsubota, MD

Study objectives: The aim of this study was to analyze various characteristics and survival in female patients treated surgically for lung cancer.

Design: Retrospective clinical study.

Patients: From 1,242 consecutive cases of primary non-small cell lung cancer treated with pulmonary resection between June 1984 and December 1998, 337 female patients (27.1%) were chosen.

Results: Female patients had the following characteristics: a significantly younger age at onset (62.5 ± 0.56 years vs 64.1 ± 0.31 years for men), a higher frequency of adenocarcinoma (86.0% vs 48.3% for men), and smaller tumors (32.7 mm vs 38.3 mm in diameter for men). Peripheral tumors were significantly more common in women than men (71.8% vs 50.6%, respectively). Among 686 patients with a history of smoking, the women smoked significantly less often (12.8% vs 91.4% for men). Complete resection was achieved significantly less often in women (79.6% vs 85.2% for men); however, women having complete resection survived significantly longer than their male counterparts. Women with a postoperative negative carcinoembryonic antigen (CEA) had a significantly better prognosis than men; however, women with a postoperative positive CEA did not. Women ≥ 60 years old survived significantly longer than their male counterparts, while women < 60 years old did not.

Conclusions: Once the tumor was resected completely, women survived longer, partly due to the influence of life expectancy. However, the incidence of malignant effusion was higher and the rate of complete resection was lower in women. (CHEST 2000; 118:1603–1609)

Key words: Brinkman index; carcinoembryonic antigen; female; lung cancer; pleural lavage; surgery; survival

Abbreviation: CEA = carcinoembryonic antigen

There has been a steady increase in the incidence of lung cancer, especially in female patients. In the 1950s, the ratio of female to male lung cancer patients was about 1:5, but by the 1980s, this had increased to about 1:2.6.1

Many reports2–8 have described survival rates in lung cancer patients with respect to gender; however, results have been controversial and confusing. The purpose of this study was to analyze various characteristics and survival in female patients treated surgically for lung cancer.

Materials and Methods

Between June 1984 and December 1998, 1,242 patients with non-small cell lung cancer underwent pulmonary resection at our institution. Of these, 337 female patients (27.1%) were studied. Histopathologic diagnosis and staging were carried out according to the new TNM staging system9 revised in 1997. In 1,022 patients with complete resections, lobectomy was by far the most common procedure and was performed in 793 patients, including 121 combined sleeve resections of the bronchus. Forty-three pneumonectomies, including 4 sleeve techniques for the tracheobronchus and 147 segmentectomies, were performed.

Immediately after thoracotomy, the pleural cavity was carefully washed with 100 mL of physical saline solution, and the fluid was examined. If the result of the cytologic examination was positive, we diagnosed the case as malignant effusion (T4).10 In this study, we excluded patients preoperatively demonstrating malignant effusion detected before operation.

Hilar and mediastinal lymph node dissection was routinely performed in patients with complete resection. Brinkman index data11 (the sum of the number of cigarettes smoked per day multiplied by years of smoking) were recorded for 686 cases (227 women and 459 men); 55.2% of all cases, and there were no differences of missing data between women and men.
in frequency. Carcinoembryonic antigen (CEA) was measured before and 1 month after the operation. The cutoff level of CEA was 5.0 ng/mL. Data were expressed as the mean ± SE.

Demographic and clinical characteristics were compared using the \( \chi^2 \) test or Student’s t test. This study was a retrospective analysis, and follow-up data were obtained for all patients. Operative mortality rates implied a 30-day postoperative mortality. Survival rate was estimated by the Kaplan-Meier method in 249 women and 654 men who had complete resection without induction therapy. The log-rank test was used to compare survival rates. A \( p < 0.05 \) was considered statistically significant. Deaths were due to cancer, noncancer causes, and unknown causes.

Results

Overall follow-up ranged from 9 to 196 months. The operative mortality rate was 0.16% (2 of 1242 patients). Significant differences between genders were found in age, histologic type, location, tumor size, resectability, smoking habit, quantities of smoking (Brinkman index), and the positive rate of CEA, but not in CEA value (Table 1). In female nonsmokers (Brinkman index, 0), adenocarcinoma accounted for 93.4%, which was significantly higher than that in female smokers (Fig 1). This relationship also held true for male patients.

The stage, T factor, and N factor with respect to gender are shown in Figures 2–4. The proportion of women patients with stage I, T1, and T4 disease was significantly higher than that of male patients.

For the 249 women with complete resection, the 5-year and 10-year survival rate was 69.0% and 51.0%, respectively, significantly higher than for male patients (Fig 5). Survival of patients in stage I or III of the disease was significantly better in women than men. For the 147 female patients with stage I adenocarcinoma, the 5-year and 10-year survival rates were 80.4% and 66.3%, respectively, significantly higher than for the male patients with the same condition (Fig 6).

In women with a postoperative CEA < 5.1 ng/mL, the 5-year and 10-year survival rates were 67.2% and 51.6%, respectively, again significantly higher than in men (Fig 7). However, in women with a postoperative CEA > 5.0 ng/mL, these rates were 31.2% and 6.2%, respectively, not significantly higher than in men (Fig 8).

### Table 1—Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Women</th>
<th>Men</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>337 (27.1)</td>
<td>905 (72.9)</td>
<td></td>
</tr>
<tr>
<td>Year of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984–1988</td>
<td>59 (24.2)</td>
<td>209 (75.8)</td>
<td></td>
</tr>
<tr>
<td>1989–1993</td>
<td>118 (28.0)</td>
<td>303 (72.0)</td>
<td></td>
</tr>
<tr>
<td>1994–1998</td>
<td>160 (28.0)</td>
<td>303 (72.0)</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>62.5 ± 0.56</td>
<td>64.1 ± 0.31</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>290 (86.0)</td>
<td>437 (48.3)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>32 (9.5)</td>
<td>411 (45.4)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Others</td>
<td>15 (4.5)</td>
<td>57 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Peripheral type</td>
<td>242 (71.8)</td>
<td>458 (50.6)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tumor diameter, mm</td>
<td>32.7 ± 0.93</td>
<td>35.3 ± 1.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tumor diameter in T4, mm</td>
<td>36.8 ± 1.19</td>
<td>46.8 ± 2.64</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Complete resection</td>
<td>249 (79.6)</td>
<td>654 (85.2)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>88 (12.8)</td>
<td>827 (91.4)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Brinkman index</td>
<td>746 ± 92.9</td>
<td>1,013 ± 26.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Preoperative CEA value, ng/mL</td>
<td>13.9 ± 2.3</td>
<td>14.8 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Positive rate, %</td>
<td>39.3</td>
<td>49.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Postoperative CEA value, ng/mL</td>
<td>5.3 ± 1.4</td>
<td>5.9 ± 0.84</td>
<td>NS</td>
</tr>
<tr>
<td>Positive rate, %</td>
<td>14.2</td>
<td>21.5</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE or No. (%) unless otherwise indicated. NS = not significant.
In female patients < 60 years old, the 5-year and 10-year survival rates were 66.3% and 56.7%, respectively, not significantly higher than in male patients of this age group (Fig 9). However, in women ≥ 60 years old, these rates were 70.4% and 50.4%, respectively, significantly higher than in the men (Fig 10).

**DISCUSSION**

We have shown that the ratio of female to male patients was similar in each period studied, even though many reports have described an increase in lung cancer in female patients. In this study, adenocarcinoma predominated over squamous cell carcinoma in female patients, whereas the two histologic types were equally common in male patients. This difference was partly attributable to a sex difference in smoking habits, with significantly more male than female smokers. This affirms the strong association between smoking and squamous cell carcinoma reported previously. Several reports have described survival rates for...
Figure 4. N factor. The ratio of N1 differs significantly between female and male patients. See Table 1 for abbreviation.

Figure 5. Actual survival curves of 903 patients with complete resection of lung cancer according to gender. Female patients had a significantly better survival curve than male patients.

Figure 6. Actual survival curves of 324 patients with stage I adenocarcinoma according to gender. Female patients had a significantly better survival curve than male patients.
Figure 7. Actual survival curves of 487 patients with the postoperative CEA $< 5.1$ ng/mL. Female patients had a significantly better survival curve than male patients.

Figure 8. Actual survival curves of 99 patients with postoperative CEA $> 5.0$ ng/mL. There was no significant difference in survival curve between genders. See Table 1 for abbreviation.

Figure 9. Actual survival curves of 256 patients ≤ 59 years old according to gender. No significant difference in survival curve was observed between genders. See Table 1 for abbreviation.
lung cancer resection with respect to gender, Ederer and Mersheimer\textsuperscript{2} in 1961, Mitsudomi et al\textsuperscript{3} in 1989, Mark et al\textsuperscript{8} in 1990, and Takahio et al\textsuperscript{7} in 1996 reported that the survival rate was higher in surgically treated female patients than in male patients, while Bignall and Martin\textsuperscript{3} in 1972, Harley\textsuperscript{5} in 1976, and Kirsh et al\textsuperscript{1} in 1982 reported the opposite. We demonstrated that the survival rate in the complete resection group was higher in female patients, regardless of stage or histologic type. The proportion of patients with T1 and T4 disease was significantly higher among women than men: T1 tumors in women were frequently located in peripheral areas and detected at an early stage, while T4 tumors showed malignant effusion. Because of malignant effusion, complete resection was achieved significantly less often in women than men, in spite of good stage I survival rates. And the T4 tumors in women were much smaller than in men. These outcomes provide the clinical impression that women apparently have lower survival rates than men. As for malignant effusion in this study, we regarded positive lavage cytologic findings as malignant pleural effusion indicating pathologic stage T4. Positivity of pleural lavage cytology is a good indicator of dissemination of lung cancer into the pleural cavity, as we reported previously.\textsuperscript{10}

If the data for the T4 cases are excluded, however, among the subjects with complete resection, women have higher survival rates. However, women < 60 years old did not survive significantly longer than that their male counterparts, whereas the women ≥ 60 years old did. These results suggest that the significant difference in survival between the genders is influenced by life expectancy. Women have a longer life expectancy (83.8 years vs 77.2 years for men).\textsuperscript{15} It is well known that the prognosis for patients with positive CEA, even after complete resection, is poor.\textsuperscript{16} Female patients with positive postoperative CEA had a significantly worse prognosis than their male counterparts, even with life expectancy taken into consideration. In the present study, once the tumor was resected completely, women survived longer than men, partly due to the influence of life expectancy. However, it should not be overlooked that the incidence of T4 was higher and the rate of complete resection was lower in women than in men.

![Figure 10. Actual survival curves of 647 patients ≥ 60 years old according to gender. Female patients had a significantly better survival curves than male patients.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21955/)

**REFERENCES**