Survival Differences by Gender for Resected Non-small Cell Lung Cancer

A Retrospective Analysis of 12,509 Cases in a Japanese Lung Cancer Registry Study

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Introduction: Women with non-small cell lung cancer (NSCLC) are more likely to have better survival than men. This study intended to assess gender differences in the survival of these patients in a large registry population.

Methods: In 2005, the Japanese Joint Committee for Lung Cancer Registration performed a nationwide retrospective registry study regarding the prognosis and clinicopathologic profiles of patients who underwent resection for primary lung neoplasms in 1999. The registry data of 12,509 patients with NSCLC were analyzed in terms of gender differences in prognosis and clinicopathologic features.

Results: There were 8353 (66.8%) men and 4156 (33.2%) women with a mean age at operation of 66.4 and 65.0 years, respectively (p < 0.001). Women had a higher incidence of adenocarcinoma (p < 0.001) and stage IA disease (p < 0.001) than men. The overall survival was significantly better in women than men. The 5-year survival rates (5-YSRs) for women and men were 75.6 and 57.9%, respectively (p = 0.0000). According to histology, the overall survival of women was significantly better than that of men for both adenocarcinoma (5-YSR, 77.7 versus 61.9%, p = 0.0000) and nonadenocarcinoma (5-YSR, 59.3 versus 53.1%, p = 0.035). In adenocarcinoma, women had a significantly better prognosis than men for pathologic stage I/II disease. However, in nonadenocarcinoma, there was no significant prognostic difference between the two genders in pathologic stage I/II disease.

Conclusions: Women with NSCLC, especially with an adenocarcinoma histology, had better survival than men. Women were more likely to have adenocarcinoma and stage IA disease, which might account for the better prognosis in women.

Key Words: Gender, Non-small cell lung cancer, Prognosis, Cancer registry.

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to clinicopathologic features and the relationship between gender and prognosis.

**PATIENTS AND METHODS**

**Registry**
In 2005, the Japanese Joint Committee for Lung Cancer Registration performed a nationwide retrospective registry study on the prognosis and clinicopathologic profiles of resected lung neoplasms in Japan. Only primary lung neoplasms that had been resected in 1999 at certified teaching hospitals in Japan were considered for the registry, which gave a follow-up period of at least 5 years. The committee received the registries of 13,344 patients from 387 teaching hospitals. The following 32 items were included in the questionnaire: gender, age, smoking status, clinical (c-) T, c-N, c-M, c-stage, preoperative treatment, surgical procedure, extent of lymph node dissection, curability, residual tumor, primary site by lobe, tumor diameter, histology, organ invasion, pathologic (p-) T, p-N, p-M, p-stage, pleural dissemination, intrapulmonary metastasis, pleural cytology, location of nodal metastasis, survival time, recurrence, and cause of death. Recurrent or multiple lung cancers were not included in this registry. Smoking status was recorded as to whether a patient was a smoker within 1 month before the operation. Operative mortality was defined as fatality from any cause within 30 days of the operation or during the same hospitalization. All patients were staged on the basis of the sixth edition of the International Union Against Cancer tumor, node, metastasis classification of the malignant tumor staging system published in 2002, and tumor histology was described according to the World Health Organization classification.

**Patients**
Sixty-nine patients (0.5%) with incomplete descriptions of their tumor histology and 655 patients (5.0%) with low-grade malignant tumors, nonepithelial tumor histology, or histology of small cell carcinoma were excluded from the study. In addition, 111 patients (0.8%) for whom gender was not given were also excluded from this study. Therefore, this study focused on the remaining 12,509 patients with non-small cell histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma).

**Statistical Analysis**
The $\chi^2$ and Student’s $t$ tests were used to evaluate the differences in categorical variables and continuous variables, respectively. The survival time was defined as the time between the date of surgery and the last follow-up date. The survival curves were estimated by the Kaplan-Meier method, and differences in survival were assessed by the log-rank test.

Overall survival (OS) was defined as the time between operation and death from any cause, except for cases of a death within 30 days of the operation and during the same hospitalization. Disease-specific survival (DSS) was defined as the time between operation and cancer-related death, where deaths from causes other than lung cancer were considered censored. Multivariate analysis by Cox’s proportional hazards ratio model was used to test the significance of prognostic factors including gender, age, smoking status (current smoker versus non-/ex-smoker), surgical procedure, histology, curability, tumor size, p-T status, and p-N status. Significance was defined as a $p$ value less than 0.05.

**RESULTS**

**Clinicopathologic Features**
There were 8353 (66.8%) men and 4156 (33.2%) women. The clinicopathologic characteristics of the genders are summarized in Table 1. There were 107 (0.9%), 29 (0.2%), 134 (1.1%), and 181 (1.4%) patients who were missing data regarding operative mode, lymph node dissection, surgical curability, and pathologic stage, respectively. These percentages were within an acceptable range as a registry database.

The mean age at surgical resection for women (65.0 years) was significantly younger than that for men (66.4 years). With regard to smoking status according to histology, the proportion of current smoker was 17.3% for men and 2.4% for women in adenocarcinoma histology ($p < 0.001$).

**TABLE 1. Characteristics of Patients with Resected Non-small Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men</th>
<th>Women</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.4 ± 9.4</td>
<td>65.0 ± 10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1598 (19.2%)</td>
<td>145 (3.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonsmoker/ex-smoker</td>
<td>6746 (80.8%)</td>
<td>3985 (96.5%)</td>
<td></td>
</tr>
<tr>
<td>Operative mode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>560 (6.7%)</td>
<td>98 (2.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>6750 (81.5%)</td>
<td>3500 (84.6%)</td>
<td>0.226</td>
</tr>
<tr>
<td>Segmentation/wedge</td>
<td>975 (11.8%)</td>
<td>537 (13.0%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Lymph node dissection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinohilar</td>
<td>6375 (76.5%)</td>
<td>3101 (74.7%)</td>
<td>0.410</td>
</tr>
<tr>
<td>Hilar only/none</td>
<td>1907 (22.9%)</td>
<td>1023 (24.7%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Unknown</td>
<td>48 (0.6)</td>
<td>26 (0.6)</td>
<td>0.732</td>
</tr>
<tr>
<td>Surgical curability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>7423 (89.9%)</td>
<td>3734 (90.7%)</td>
<td>0.736</td>
</tr>
<tr>
<td>Incomplete</td>
<td>735 (8.9%)</td>
<td>320 (7.8%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Unknown</td>
<td>101 (1.2%)</td>
<td>62 (1.5%)</td>
<td>0.199</td>
</tr>
<tr>
<td>Operative mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>222 (2.7%)</td>
<td>31 (0.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>4498 (53.9%)</td>
<td>3670 (88.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3305 (39.6%)</td>
<td>359 (8.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>403 (4.8%)</td>
<td>69 (1.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adenosquamous cell carcinoma</td>
<td>145 (1.7%)</td>
<td>58 (1.4%)</td>
<td>0.162</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>2627 (31.9%)</td>
<td>2105 (51.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IB</td>
<td>1912 (23.2%)</td>
<td>694 (16.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IIA</td>
<td>255 (3.1%)</td>
<td>105 (2.6%)</td>
<td>0.106</td>
</tr>
<tr>
<td>IIB</td>
<td>1074 (13.1%)</td>
<td>242 (5.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IIIA</td>
<td>1349 (16.4%)</td>
<td>498 (12.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IIB/IV</td>
<td>1014 (12.3%)</td>
<td>453 (11.1%)</td>
<td>0.070</td>
</tr>
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</table>
nonadenocarcinoma histology, the proportion of current smoker was 21.3% for men and 12.1% for women ($p < 0.001$). In addition, the proportion of current smoker in women also showed significant difference between histologic types (adenocarcinoma versus nonadenocarcinoma) ($p < 0.001$), and the difference between histologic types was also significant in men ($p < 0.001$). Deaths within 30 days of the operation, which were included in operative mortality, were 97 patients (1.2%) for men and 22 (0.5%) for women ($p < 0.001$). Although adenocarcinoma was the most common histologic type in both genders, the distribution of histologic types was significantly different between the genders. The distribution according to histologic type in men and women is shown in Figure 1. Women had significantly more adenocarcinoma ($p < 0.001$) and less squamous cell carcinoma ($p < 0.001$) than men. As for the pathologic stage, women had a significantly higher incidence of stage IA disease than men ($p < 0.001$).

**Survival by Gender**

The overall 5-year survival rates (5-YSRs) for men and women were 57.9 and 75.6%, respectively. The survival curves are shown in Figure 2. Women had significantly better survival than men ($p = 0.0000$). According to the histologic type, women had significantly better overall survival (OS) than men with adenocarcinoma (5-YSR, 77.7 versus 61.9%, $p = 0.0000$). In nonadenocarcinoma, women again had significantly better OS than men (5-YSR, 53.1% versus 59.3%, $p = 0.035$) (Figure 3). The prognosis between women and men was further studied with regard to histologic type and pathologic stage. In patients with adenocarcinoma histology and pathologic stage I/II disease, women had significantly better OS than men (Figures 4A and 5A). In contrast, there was no significant OS difference between the genders among
patients with nonadenocarcinoma histology and pathologic stage I/II disease (Figures 4 and 5).

Disease-specific 5-YSRs for men and women were 64.9 and 79.2%, respectively (Figure 6). Women had significantly better DSS than men \( (p = 0.0000) \). The 5-year survival rate for pathologic stage I in adenocarcinoma was 78.6% for male patients and 90.0% for female patients \( (p = 0.0000) \). The 5-year survival rate for pathologic stage I in nonadenocarcinoma was 65.4% for male patients and 72.8% for female patients \( (p = 0.058) \).

**FIGURE 4.** Overall survival curves according to gender of pathologic stage I in adenocarcinoma (A) and nonadenocarcinoma (B). The 5-year survival rate for pathologic stage I in adenocarcinoma is 78.6% for male patients and 90.0% for female patients \( (p = 0.0000) \). The 5-year survival rate for pathologic stage I in nonadenocarcinoma is 65.4% for male patients and 72.8% for female patients \( (p = 0.058) \).

In a Cox proportional hazards model to predict OS, the following factors persisted as important prognostic factors: gender, age, surgical procedure, histology, curability, tumor size, p-T status, and p-N status (Table 2). Gender had impact on survival with relative risk for women of 0.63 \( (p = 0.0000) \) and 95% confidence interval 0.58–0.68. Smoking status was not statistically significant or important determinant of survival, with relative risk for current smoker of 1.00 \( (p = 0.94; 95\% \text{ confidence interval } 0.93–1.09) \).

**DISCUSSION**

In this Japanese Lung Cancer Registry Study of 12,509 patients with resected NSCLC, women showed significantly better survival than men after resection. Female gender was one of the statistically positive independent predictors of survival in this registry. This better survival for women was observed regardless of the histologic type (adenocarcinoma or nonadenocarcinoma). Many other studies that have evaluated the effect of gender on the lung cancer prognosis have also suggested that women have a survival advantage, but the reasons for this survival advantage have remained unknown. Genetic, metabolic, and hormonal factors have been proposed as potential explanations for the survival benefit experienced by women.
resected NSCLC in females was stage IA disease. In Japan, there have been opportunities of resecting small-sized lung cancers since a computed tomography (CT) screening for lung cancer was introduced in early 1990s. Most of the lung cancers detected by CT screening were likely to be small-sized and slow-growing adenocarcinomas.24,25 In addition, people with lung cancer detected by CT screening accounted for a large proportion of women.26 This would be one of the reasons for the increased incidence of early-stage lung cancers among women. In fact, it has been reported that early-stage lung cancers such as bronchioloalveolar carcinoma or adenocarcinoma mixed bronchioloalveolar subtype tend to occur frequently in nonsmoking women.27,28 These data indicated that the difference in the pathobiologic characteristics of adenocarcinoma between genders should be addressed.

The increased incidence of adenocarcinoma among women may be attributed to several causes, including genetic, biologic, and environmental factors. Genetic polymorphisms and the mutation of specific genes have been examined as possible causes of the predominance of the adenocarcinoma histology in women.29–31 Epidermal growth factor receptor and K-ras gene mutations have been detected more commonly in women than men and have been found mainly in adenocarcinomas of the lung.29–32 Several reports33,34 have investigated the relationship between the hormonal effects of estrogen and the development of lung cancer, especially adenocarcinoma, because the obvious biologic differences between men and women are hormonal. These findings in this study and the literature also suggest that the pathway of carcinogenesis might be different between women and men.

On the other hand, we observed that women with adenocarcinoma had a significantly better prognosis in both stage I disease and stage II disease, whereas there was no significant gender difference in nonadenocarcinoma patients with either stage I or stage II. Based on the fact that adenocarcinoma was more common in women and they have better
The proportion of smokers for men is still higher than that for women, although it has been reducing little by little. Smoking is also closely related to cardiovascular and pulmonary diseases, e.g., ischemic heart disease, cerebrovascular disorder, and pulmonary emphysema. These diseases might lead to noncancerous death before cancer-specific death. Thus, the better prognosis in women among patients with adenocarcinoma might be partially attributed to the differences in the incidence of noncancerous death between genders because women would include fewer smokers than men. In fact, Chang et al. reported that the female-gender advantage in survival for resected NSCLC changed to no survival advantage for females after propensity score matching (variables: age, smoking status, histologic types, and pathologic stages) between males and females. Hanagiri et al. showed that there was no gender difference in cancer-related survival regardless of a significant female-gender advantage in OS for patients with resected lung adenocarcinoma.

In this registry study, according to relationship between prognosis and the combination of histologic type and pathologic stage, women had significantly better DSS than men only in patients with adenocarcinoma histology and pathologic stage I disease. Therefore, at the least, deaths of causes other than lung cancer are likely to affect survival difference between genders except for patients with stage I adenocarcinoma. A significant female-gender advantage in stage I adenocarcinoma persisted in DSS and OS. Stage I adenocarcinoma in women would presumably include many bronchioalveolar carcinomas, which tend to occur often in nonsmoking women, although histologic subtypes in adenocarcinoma was recorded in this registry.

Although the identification of factors that predispose to operative mortality is beyond the scope of this study, an older age at surgical resection and a higher number of pneumonectomies for men could be related to the higher 30-day mortality among men in this series. The higher operative mortality rate in male patients with lung cancer has been previously reported.
In conclusion, we found that women showed significantly better 5-year survival than men after surgical resection of NSCLC. Especially in adenocarcinoma, the survival advantage for women was significant in pathologic stages I and II, whereas in nonadenocarcinoma, this gender difference was not significant in pathologic stage I or II. Although adenocarcinoma is the most common histologic type in both genders, the proportion of adenocarcinoma and stage IA disease in women was much greater than that in men. The incidence of early-stage adenocarcinoma might reasonably account for a better prognosis in women as a whole. Further studies should focus on the identification of differences in the pathobiological nature of early lung adenocarcinoma between women and men.

REFERENCES