Gender difference in survival of resected non-small cell lung cancer: Histology-related phenomenon?

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Objective: It remains controversial whether there is a gender difference in survival of patients with resected non-small cell lung cancer.

Methods: We retrospectively analyzed 2770 patients (1689 men and 1081 women) with non-small cell lung cancer who underwent pulmonary resection between 1995 and 2005 at the National Cancer Center Hospital, Tokyo. A gender difference in survival was studied in all patients, in those divided according to histology or pathologic stage, and in propensity-matched gender pairs.

Results: There were no differences in background, such as preoperative pulmonary function, operation procedures, or operative mortality. The proportions of adenocarcinoma and pathologic stage I in women were greater than those in men (93.6% vs 61.7% and 71.4% vs 58.6%, respectively) ($P < .001$). Overall 5-year survival of women was better than that of men (81% vs 70%, $P < .001$). In adenocarcinoma, the overall 5-year survival for women was better than that for men in pathologic stage I (95% vs 87%, $P < .001$) and in pathologic stage II or higher (58% vs 51%, $P = .017$). In non-adenocarcinoma, there was no significant gender difference in survival in pathologic stage I ($P = .313$) or pathologic stage II or higher ($P = .770$). The variables such as age, smoking status, histology, and pathologic stage were used for propensity score matching, and survival analysis of propensity score-matched gender pairs did not show a significant difference ($P = .69$).

Conclusion: Women had better survival than men; however, there was no survival advantage in propensity-matched gender pairs. A gender difference in survival was observed only in the adenocarcinoma subset, suggesting pathobiology in adenocarcinoma in women might be different from that of men.

Most studies on gender-associated differences in lung cancer have found that women have several characteristics that are different from those in men, such as younger age at presentation, larger proportions of nonsmokers and early-stage diseases, and predominance of adenocarcinoma.¹⁻⁶ However, the influence of female gender on survival remains controversial because it has been insisted that gender is not a significant prognostic factor in non-small cell lung cancer (NSCLC), although gender has been associated with smoking exposure, stage, histologic subtype, and therapeutic management.^{7,8}

We believe that a unique analysis with a large database may help to clarify the influence of gender on survival. The purpose of this study is to explore gender differences in clinical characteristics and survival based on a retrospective analysis of patients with NSCLC who had undergone lung resection in a single institute during an 11-year period.

MATERIALS AND METHODS

From January 1995 to December 2005, 2800 patients underwent lung resection for primary lung cancer at the National Cancer Center Hospital, Tokyo. Among these, 2770 patients (1689 men and 1081 women) who underwent lung resection for NSCLC were reviewed retrospectively. This study was approved by the institutional review board.

Preoperative evaluation was done by means of history and physical examination, posteroanterior and lateral chest radiographs, and blood tests, including complete blood count and serum chemistries. Computed tomography scans of the chest and upper abdomen (including the liver and adrenal glands) were checked routinely. Bone scintigraphy and brain imaging were performed in cases of suspicious symptoms. A pulmonary function test and electrocardiography were checked routinely. Quantitative pulmonary ventilation and perfusion scan were performed in patients with marginal pulmonary function. The evaluation of chronic diseases and consultation with the corresponding physicians depended on the patients' conditions.

Patients with clinical stages I and II and selected cases of stage IIIA underwent lung resection via thoracotomy. Basically, neoadjuvant preoperative therapy was not performed except for recent cases of superior sulcus tumor. Patients with N2 disease that was detected intraoperatively received postoperative adjuvant therapy. All patients were staged on the basis of the *International Union Against Cancer TNM Classification of Malignant Tumors* staging system published in 1997,⁹ and tumor histology was described according to the World Health Organization classification.¹⁰ For tumors of adenocarcinoma with a greatest dimension of 2 cm or less, Noguchi and colleagues' classification¹¹ was used to describe the histopathologic details. Types A and B correspond to bronchoalveolar carcinoma in the World Health Organization classification, whereas type C corresponds to adenocarcinoma with mixed subtypes, including bronchoalveolar carcinoma and invasive adenocarcinoma. Types D, E, and F correspond to invasive solid, acinar, and papillary adenocarcinoma, respectively.

Follow-up was achieved through periodic visits to the outpatient clinic until the present time or patient's death. Operative mortality was defined as death during hospitalization for lung resection or within 30 days of operation.

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Abbreviation and Acronym

NSCLC = non-small cell lung cancer

The chi-square test was used to evaluate the significance of observed differences in the proportions of patients in the various outcome categories. Survival was measured from the date of operation, and the median survival was calculated and plotted according to the Kaplan–Meier method. Differences in survivals between groups were compared with the log-rank test.

For balanced assignment of the included patients to correct gender confounding in survival, propensity score matching was used. The variables such as age (continuous), smoking status (ever or never), histologic types (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or others), and pathologic stages (I, II, III, or IV) were used. These were selected on the basis of their significant difference between both genders (Table 1). A coefficient that was calculated by logistic regression analysis was multiplied to each variable, and the sum of these values were the propensity score for individual patient.¹² Gender pairs with equivalent propensity score were selected by a 1-to-1 match. All survival comparisons and analyses were performed using SigmaPlot (Systat Software Inc, San Jose, Calif).

RESULTS**Clinical Features, Histology, and Pathologic Staging**

The clinical characteristics of 2770 patients are summarized in Table 1. The distribution of histologic subtypes was significantly different between the 2 genders: There was more adenocarcinoma (93.6% vs 61.7%, $P < .001$) and less squamous cell carcinoma (4.1% vs 30.3%, $P < .001$) in women. The distribution of pathologic stages showed a statistically significant gender difference in that women had a disproportionate representation in stage I disease compared with men (71.4% vs 58.6%, $P < .001$) (Table 1).

With regard to adenocarcinoma, which was the most frequent histology ($n = 2054$, 74.2%), there was a significant difference in pathologic features between men and women. There were more well-differentiated tumors ($P < .001$) in women but more lymphatic ($P = .011$) or vascular invasion ($P < .001$) in men (Table 2). There were 844 T1 adenocarcinomas with a greatest dimension of less than 2 cm, and information regarding Noguchi's types was available in 604 cases (71.6%). Women had more Noguchi's type A or B ($P = .000$) and less Noguchi's type D, E, or F ($P = .000$) (Figure 1).

Survival Analysis

Overall 5-year survivals for men and women were 70% and 81%, respectively (Figure 2), and there was a statistically significant gender difference in survival ($P < .001$). In adenocarcinoma, the overall 5-year survival was 84% for women ($n = 1012$) and 75% for men ($n = 1042$) ($P < .001$). However, there was no significant gender difference in survival in non-adenocarcinoma ($P = .299$) (Figure 3). When the patients were divided into subsets according to the combination of histology and pathologic stage, overall

TABLE 1. Characteristics of patients ($n = 2770$) with resected non-small cell lung cancer

	Men ($n = 1689$)	Women ($n = 1081$)	<i>P</i> value
Age (y)	64.8	62.8	<.001
FEV _{1.0} (%)	76.8 ± 21.6	82.5 ± 12.7	.33
Ever-smoker (%)	77.5	22	<.001
Elevated CEA level ^a (%)	28.2	21	<.001
Operative procedures			
Wedge resection + Segmentectomy	189 (11.2%)	134 (12.4%)	.877
Lobectomy	1381 (81.8%)	921 (85.2%)	.38
Pneumonectomy	119 (7.0%)	26 (2.4%)	.665
Morbidity/mortality			
Mortality	11 (0.65%)	6 (0.65%)	.392
Serious complications ^b	11 (0.7%)	5 (0.5%)	.523
Empyema with or without BPF	34 (2%)	4 (0.4%)	<.001
Histology			
Adenocarcinoma	1042 (61.7%)	1012 (93.6%)	<.001
Squamous cell carcinoma	511 (30.3%)	44 (4.1%)	<.001
Large cell carcinoma	97 (5.7%)	10 (0.9%)	<.001
Others	39 (2.3%)	15 (1.4%)	.077
Pathologic stage			
CIS	2 (0.1%)	1 (0.1%)	
p stage I	990 (58.6%)	772 (71.4%)	<.001
p stage II	320 (18.9%)	111 (10.3%)	<.001
p stage III	361 (21.4%)	190 (17.6%)	.014
p stage IV	16 (1%)	7 (0.6%)	.385

FEV, Forced expiratory volume; CEA, carcinoembryonic antigen; BPF, bronchopleural fistula; CIS, carcinoma in situ. ^aPreoperative CEA level > 5 ng/mL. ^bRespiratory complications that required ventilator assistance, cerebrovascular accident, congestive heart failure, or acute myocardial infarction.

5-year survival of women was significantly better than that of men in pathologic stage I (95% vs 87%, $P < .001$) and pathologic stage II or higher (58% vs 51%, $P = .017$) within adenocarcinoma (Figures 4, A and 5, A). On the other hand, there was no significant gender difference in survival in pathologic stage I (79% in men vs 74% in women, $P = .313$) or pathologic stage II or higher (50% in men vs 48% in women, $P = .770$) within non-adenocarcinoma (Figures 4, B and 5, B).

TABLE 2. Pathologic features of adenocarcinoma according to gender status ($n = 2054$)

	Male ($n = 1042$)	Female ($n = 1012$)	<i>P</i> value
Differentiation			
Well	524 (50.3%)	678 (67%)	<.001
Moderate	345 (33.1%)	283 (28%)	.11
Poor	173 (16.6%)	51 (5%)	<.001
Lymphatic invasion			
Present	489 (46.9%)	396 (39.1%)	.011
Vascular invasion			
Present	510 (48.9%)	369 (36.5%)	<.001

FIGURE 1. Distribution of Noguchi’s type for smaller adenocarcinoma according to gender. There are significantly more Noguchi’s type A or B in women and more Noguchi’s type D, E, or F in men.

Propensity Score Matching

The distribution of characteristics of propensity score-matched gender pairs (n = 539) were summarized in Table 3. They were well-matched gender pairs without significant difference in clinical characteristics. There was no significant gender difference in survival in propensity score-matched gender pairs ($P = .69$) (Figure 6).

DISCUSSION

We observed a significant survival difference between men and women without notable differences in background, such as preoperative pulmonary function, type of operation procedure, or operative mortality. Although the better survival of women in the present study is consistent with several previous reports (Table 4), it can be inferred from the survival analysis of propensity score-matched gender pairs that gender is a marker of a certain risk group with different tumorigenesis rather than an independent prognostic indicator.

Several factors can be considered to be interrelated with the better survival of women: 1) histopathology; 2) internal environment, such as hormonal or genetic status; and 3) innate demographic characteristics or artifactual factors. It has been reported that the impact of tumor histology on survival is unclear. Alexiou and colleagues¹³ showed that squamous cell type was an independent favorable predictor of survival, whereas others have shown no survival difference based on the cell type.¹⁴ Women showed a significantly larger proportion of well-differentiated type adenocarcinoma (Table 2) and Noguchi’s classification A or B (Figure 1). A high degree of differentiation provides a relative survival advantage,¹⁵ and survival is significantly longer even in patients after recurrence with well-differentiated tumors than in those with moderately or poorly differentiated tumors.¹⁶ The degree of differentiation is related to the expression of tumor suppressor gene, such as WW domain-containing oxidoreductase, and the reduced or absent expression of this gene was observed in invasive adenocarcinoma.¹⁷ These results reflect the notion that the degree of differentiation is related

to biological aggressiveness at a genetic level. It is also supported by the report that epidermal growth factor receptor mutation was correlated with subtypes of adenocarcinoma and their histologic grade.¹⁸ On the basis of the subset analyses according to the histology and survival analysis in propensity score matching, histology is assumed to be one of the factors affecting the gender difference in survival.

The distinctive internal environment of women might be related to their better survival. It has been reported that gender-dependent differences in estrogen receptor alpha and beta expression could contribute to unique phenotypic characteristics of lung cancer in women.¹⁹ Likewise, parathyroid hormone-related protein, which predicts longer survival in women but not in men, showed a more intense tumor suppression effect in an NSCLC model in female mice because it was regulated negatively by androgen hormone.²⁰ Along with hormonal influences, genes such as $p53^{R172H?gH+}$ $K-ras^{LA1/+}$ have been recognized to be associated with aggressive behavior and even a gender difference in cancer-related death.²¹

FIGURE 2. Survival curves according to gender. The overall 5-year survival is 81% for women (n = 1081) and 70% for men (n = 1689). Women show significantly better survival than men ($P < .001$).

FIGURE 3. Survival curves according to gender in adenocarcinoma (A) and non-adenocarcinoma (B). In adenocarcinoma, the overall 5-year survival is 75% for men ($n = 1042$) and 84% for women ($n = 1012$). This gender difference is significant ($P < .001$). In non-adenocarcinoma, the overall 5-year survivals of men ($n = 647$) and women ($n = 69$) are 64% and 58%, respectively. This gender difference in survival is not significant ($P = .299$).

Several artifactual factors might be related to the gender difference in survival.²² The demographics of Japan are changing so rapidly that life expectancy is increasing for women. Furthermore, a favorable mix of demographic variables, such as good performance status, more asymptomatic or screen-detected diseases, and fewer comorbidities, might affect the better survival of women, although such information was not available in this study.

One of the most remarkable results of this study is that women show better survival than men even within subsets of the same pathologic stage within adenocarcinoma, but on the other hand no difference was observed in non-adenocarcinoma subsets. One possible explanation for this result is

a difference in smoking status. In contrast with non-adenocarcinoma, in most cases, adenocarcinoma in women arises in the absence of the carcinogenic effect of tobacco, or at least under the influence of only secondhand smoke from the spouse or workplace. This could be responsible for the difference in tumorigenesis and pathobiological activity of adenocarcinoma in women. In addition to this difference in smoking status, women are often exposed to different external environments, such as cooking fumes from fuels and oils, household pollutants, and industrial dust. Ko and colleagues²³ suggested that the frequency of exposure to fumes from cooking oils, when not reduced by an extractor, might be an important factor in lung cancer in nonsmoking women.

FIGURE 4. Survival curves according to gender of pathologic stage I in adenocarcinoma (A) and non-adenocarcinoma (B). The overall 5-year survival of pathologic I in adenocarcinoma for women is significantly better than that for men (95% vs 87%, $P < .001$). There is no significant gender difference in survival of pathologic stage I in non-adenocarcinoma (79% vs 74%, $P = .313$).

FIGURE 5. Survival curves according to gender of pathologic stage II or higher in adenocarcinoma (A) and non-adenocarcinoma (B). There is a significant gender difference in survival in the subset of adenocarcinoma (57% in women, 51% in men, $P = .017$), but not in non-adenocarcinoma (50% in men, 48% in women, $P = .770$).

TABLE 3. Characteristics of propensity-matched gender pairs (n = 1078)

	Men (n = 539)	Women (n = 539)	P value
Age (y)	63.4	62.8	.07
Ever-smoker	259 (48.1%)	238 (44.2%)	.22
Adenocarcinoma	448 (83.1%)	450 (83.5%)	.92
p stage I	350 (64.9%)	355 (65.9%)	.78

FIGURE 6. Survival curves of propensity score matched-gender pairs. There is no significant gender difference in survival ($P = .69$).

Complicated interactions in the external environment may underlie the difference in adenocarcinoma in women.

On the basis of the results regarding gender differences in the pathologic features of adenocarcinoma or survival analyses in subsets, adenocarcinoma in women is presumed to have different pathobiologic behaviors from that in men. Genetic polymorphisms, familial susceptibility, and the mutation of specific genes are now being investigated as

TABLE 4. Reports describing a gender difference in survival in lung cancer

Authors	Year	Years analyzed	Gender difference in survival	Comments
Ferguson and colleagues ¹	2000	1980–1998	$P = .006$	
Alexiou and colleagues ¹³	2002	1990–2000	$P = .001$	Lower operative mortality in women
Cerfolio and colleagues ³	2006	1998–2005	$P < .001$	Stages I, II, and III NSCLC
Foegle and colleagues ⁷	2007	1982–1997	$P = .84$	
Asamura and colleagues ⁴	2008	1999	$P = .000$	

possible causes of the biological differences in adenocarcinoma in women.^{24–26} Further investigations are needed on the pathologic and biological nature of adenocarcinoma in women.

CONCLUSIONS

There is significant gender difference in survival after resection of NSCLC. Women show significantly better overall 5-year survival than men in all patients and in subsets of adenocarcinoma within the same pathologic stage, but there was no survival advantage of women in propensity-matched gender pairs. The pathobiology in adenocarcinoma in women might be different from that in men.

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