ORIGINAL ARTICLE

Long-term survival in lung cancer after surgical treatment: is gender a prognostic factor?

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Background: In a prior study, we found a possible correlation between gender and prognosis in non-small cell stage I lung cancer (NSCLC), showing a better survival rate among females. This is in accordance with some other reported studies. The purpose of this study was to further clarify the role of gender as a possible prognostic factor in NSCLC.

Patients and Methods: In a retrospective cohort study, we assessed survival in 163 NSCLC patients who underwent surgical curative treatment at PUCRS Hospital between 1990 and 1997. The cohort consisted of 124 (76.07%) males and 39 (23.93%) females. Data were analyzed using Kaplan-Meier plots. We also used the Mann-Whitney test for comparison of survival times between and among groups and the Cox regression model to adjust for potential confounding factors.

Results: Median survival was 32.3 for males and 60.6 months for females, and the 5-year survival rates were 38.0% and 55.4%, respectively (p = 0.030). Considering only patients at stage I, survival rates were 44.4% for men and 81.8% for women (p = 0.009). Cox regression showed that a gender effect was still evident after adjustment for several factors (age, hemoglobin, histology, tumor size, surgery type and postoperative complications). The hazard ratio for women compared to men was 0.09 (90% CI = 0.03-0.25; p < 0.001).

Conclusion: This study confirms our previous findings that women live longer after NSCLC surgery than do men. This effect is observed only in cases of early-stage cancer and withstands adjustment for various factors.

Keywords: **Lung cancer. Long-term survival. Gender-related differences. Prognostic factors.**

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***Abbreviations used in this paper*:**
NSCLC – Non-small cell lung cancer
PUCRS – Pontifícia Universidade Católica do Rio Grande do Sul
TNM – Tumor-node-metastasis (staging)

INTRODUCTION

Worldwide, lung cancer is by far the most common cancer in males (responsible for 18% of all new cases) and is also quite frequent in females.[1,2] Although the incidence in males plateaued in the 1980s and 1990s, it has been steadily decreasing since then, whereas lung cancer rates among women have increased by more than 500% since 1950 and continue to climb.[3]

Lung cancer is also the leading cause of cancer death in many countries. Although breast cancer is more frequent, lung cancer is associated to a poorer prognostic. Death rates due to lung cancer in

women will probably continue to increase for at least the next decade since the female smoker population is now reaching the age at which the risk for such neoplasms increases.[4]

In Brazil, there are approximately 20,000 new cases of lung cancer each year. In 1999, there were 14,127 deaths due to lung cancer, a mortality rate of 8.62/100,000. In recent years, there has been a steep increase in the incidence of lung cancer deaths in women, from 4.19/100,000 in 1994 to 5.18/100,000 in 1999.[5,6]

Some authors have reported a more favorable prognosis for lung cancer in women than in men.[7-12] In a previous study of cases of stage I non-small cell lung cancer (NSCLC), we also reported significant gender-related differences in long-term survival, with better rates among females. This difference remained significant even after adjustment for other factors (age, hemoglobin, postoperative complications, histology and tumor size).[13]

To better characterize such gender differences in lung cancer survival, additional clinical information was collected about patients undergoing surgery for non-small cell lung cancer between 1990 and 1997. In this study, we analyze this cohort of patients.

PATIENTS AND METHODS

We studied patients with non-small cell lung cancer who underwent surgical curative resection between January 1, 1990 and December 31, 1997 at the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS) Hospital São Lucas in Porto Alegre, Brazil. Data was collected through review of medical records, which included patient data such as age, sex, smoking habits, hemoglobin, tumor size, histology, tumor-node-metastasis (TNM) staging, postoperative complications, surgery type, date of surgery, date of last medical visit and, if applicable, date of death (for survival analysis). The PUCRS Research Ethics Committee approved the study.

Histologic confirmation was obtained in all patients. All patients were classified through TNM staging.[14] The same staff of thoracic surgeons performed all surgical procedures and the choice of resection type was dictated by local extent of tumor and secondarily by cardiorespiratory function and general status. Follow-up information was obtained by examination of death certificates from the Rio Grande do Sul State Death Registry, from hospital charts or through active follow up (phone calls to patient families). Survival rates were calculated from date of surgery until death or until the end of the study period.

Patients were divided into two groups by gender and compared with regard to demographic, clinical and histopathologic characteristics, as well as to long-term survival rates (5 years). The distribution of these variables in both sexes was compared using the chi-square test for categorical variables and Student's *t* test for continuous variables. Survival was determined by the Kaplan-Meier method.[15] Differences in survival rates between groups were tested for significance using the log-rank test. All variables were included in the univariate analysis, considering long-term survival as the end point. A regression analysis based on the Cox proportional hazards model was conducted using selected covariates correlated with outcome.[16] Independent effects of stage, sex, age, histology, tumor size, surgery type, hemoglobin, and postoperative complications were determined.

Descriptive statistics are expressed as mean ± standard deviation. Statistical significance was set to $p \leq 0.05$. All of the above-mentioned analyses were performed using SPSS for Windows version 10.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

During the period studied, lung resections were performed in 163 patients with non-small cell lung cancer, of whom 124 (76.07%) were male. The mean age was 60.9 ± 8.9 (range, 32-80). No significant gender-related differences were found among the variables studied, except that there were fewer female smokers than male smokers. Hemoglobin was also different between genders, but without clinical significance. The main patient characteristics are listed by gender in Table I.

At the end of 5 years of post-surgical follow up, 55.4% of the women and 38.0% of the men were still living (p = 0.030). The median overall survival was 41.5 months, with an interquartile range of 11.4 to 63.8 months. In women, the median was 60.6 months (interquartile range, 28.8 to 96.9 months), and it was 32.3 months in men (interquartile range, 9.8 to 62.2 months) (p = 0.014).

When considering only stage I patients in the univariate analysis, 5-year survival was greater in females (81.8%) than in males (44.4%) (p = 0.009). The median survival among women in this subgroup of patients was 84.7 months (interquartile range, 60.5 to 113.3 months), whereas it was 44.9 months in men (interquartile range, 15.7 to 84.9 months) (p = 0.002; Figure 1). For patients in stages II or higher, the difference between genders was not statistically significant (p = 0.634).

Table 2 shows that this gender-related difference remained in effect even after adjustment for several potential confounding factors considered in this study, with a relative risk (RR) of 0.09. Another factor that was significantly correlated with survival was hemoglobin level, with a small protective effect (RR = 0.7). Age was also protective, although not to a statistically significant degree. Postoperative complications had an RR of 3.43. Other factors were not statistically significant.

DISCUSSION

It is well known that tumor stage at time of surgery plays a role in survival of lung cancer patients. However, this and other factors, such as age, histologic type and type of surgery, are usually reported without regard to gender.[17]

In this study, we observed that female gender exerted a significant positive effect on survival following lung resection for non-small cell lung cancer. When survival in months and 5-year survival rates were analyzed according to gender, this effect was statistically and clinically significant.

Female survival rates were significantly higher in cases of stage I non-small cell lung cancer, but not in more advanced cases. Similar results have been reported by Perrot et al.[12] , as well as, more recently, by Ferguson et al.[10] and Alexiou et al.[7]

Since the 1980s, a few large database studies by cooperative groups have purported that female sex could be an independent positive predictor of survival in lung cancer cases, especially in cases of limited disease.[9,18] During the same period, Johnson et al.[11] reported that women who had small cell lung carcinoma and were treated with chemotherapy had better survival rates than men who were similarly treated. Ouellette et al.[19] found a statistically significant difference in lung cancer survival favoring women when adjusted for stage.

We have previously investigated the role of sex as a prognostic factor, using a 5-year survival multivariate analysis that considered age, stage and histologic type as related factors.[13] We found a similar overall survival between the two genders, although, in cases of stage I cancer, there was a significant advantage for women.

In the present study, sample size was increased and the study period was extended. In confirmation of our previous findings, we found 5-year survival rates to be 81.8% for females and 44.4% for males (p = 0.009). In cases of stage I lung cancer, women lived 40 months longer than men, considering the difference of the median survival between both genders. Gender effect was still present after Cox regression adjustment for sub-stage, age, smoking habits, hemoglobin, histology, tumor size, surgery type and postoperative complications. Postoperative complications, age and some histological types had negative effects on prognosis, although not statistically significant. In contrast, normal value of hemoglobin, used as an indirect marker of performance status, was a protective factor, although of little magnitude.

There were no significant differences between the two genders regarding most of factors studied. On average, female patients were younger, as has been found in other studies.[8,12,19] However, this feature was not statistically significant.

There was a significant difference in the percentage of smokers among women (78.9%) compared to men (98.3%), in agreement with the findings of most other studies.[10-12] In order to avoid introducing a bias, the few non-smokers in this sample were excluded from the analysis.

Stage is a well-known factor related to survival among tumor-related factors. Some histologic types are implicated in prognosis. Survival rates have been shown to be higher in cases of adenocarcinoma of the lung than in cases of squamous-cell cancer.[10,20] However, there is some controversy concerning this finding. For example, neither Mountain et al.[21] nor Martini et al.[22] were able to reproduce this. In this study, we also found no such difference.

Performance status is usually used as clinical predictor of outcome in lung cancer.[17,20] However, this parameter was not recorded in all charts included in this retrospective study. Therefore, an attempt of such evaluation was made using hemoglobin level as a marker of the general conditions of the patient, a method previously suggested.[17] Anemia has been reported to have a negative impact on survival of lung cancer patients receiving chemotherapy or radiation therapy.[17,23] In our patients, normal hemoglobin level had a positive effect on outcomes in stage I patients.

Scant information exists regarding such gender-related differences in lung cancer, as this line of research has only recently been opened.[24-27]

The reasons for such findings are not well understood, but women appear to be more susceptible to developing lung cancer, even though they start smoking later and smoke less than men. It has been suggested that there may be a hormonal component and that interaction between estrogens and smoking needs to be studied further.[12] There is evidence suggesting that the growth of tumor cells may be dependent on reproductive hormones and that non-small cell lung cancer cancers have an abundance of estrogen receptors.[24] This could explain the correlation between lung cancer and gender. These receptors differ among the various types of lung carcinoma and stages of disease.[25]

If others confirm our findings, it is possible that extrapolation of stage I NSCLC survival results based on data that does not take gender into account may result in an underestimation of long-term survival rates in females. This method my need to be reevaluated. In this study, we have shown that women live longer after surgery for non-small cell lung cancer than do men. This difference remained in effect after the adjustment for several factors.

REFERENCES

1. **Bray F, Sankila R, Feraly J, Parkin DM: Estimates of cancer incidence and mortality in Europe. Eur J Cancer 2002;38:99-166.**
2. **Skuladottir J, Olsen JH: Epidemiology of lung cancer. Eur Respir Monograph 2001;6:1-12.**
3. **Loewen GM, Romano CF: Lung cancer in women. J Psychoactive Drugs 1989;21:319-321.**
4. **Tanoue LT: Cigarette smoking and women's respiratory health. Clin Chest Med 2000;21:47-66.**
5. **Uehara C, Santoro IL, Jamnik S: Cancer de pulmão: comparação entre os sexos. J Pneumol 2000;26:286-290.**
6. **Ministério da Saúde: Informações em saúde: indicadores e dados básicos. www.datasus.gov.br 2002.**
7. **Alexiou C, Onyeaka CV, Beggs D, Akar R, Beggs L, Salama FD, Duffy JP, Morgan WE: Do women live longer following lung resection for carcinoma? Eur J Cardio-thorac Surg 2002;21:319-325.**
8. **Bouchardy C, Fioretta G, Perrot M, Obradovic A: Determinants of long term survival after surgery for cancer of the lung. Cancer 1999;86:2229-2237.**
9. **Ferguson MK, Skosey C, Hoffman PC, Golomb HM: Sex-associated differences in presentation and survival in patients with lung cancer. J Clin Oncol 1990;8:1402-1407.**
10. **Ferguson MK, Wang J, Hoffman PC, Haraf DJ, Olak J, Masters GA, Vokes EE: Sex-associated differences in survival of patients undergoing resection for lung cancer. Ann Thorac Surg 2000;69:245-250.**
11. **Johnson BE, Steinberg SM, Phelps R, Edison M, Veach SR, Ihde DC: Female patients with small cell lung cancer live longer than male patients. Am J Med 1988;85:194-196.**
12. **Perrot M, Licker M, Bouchardy C, Usel M, Robert J, Spiliopoulos A: Sex differences in presentatioin, management and prognosis of patients with non-small cell lung carcinoma. J Thorac Cardiovasc Surg 2000;119:21-26.**
13. **Chatkin JM, Abreu CM, Crossetti TO, Pinto JAF, Chatkin G, Padilha DA, Wagner MB, Fritscher CC: Is gender a prognostic factor in long term survival non-small cell lung cancer? Eur Respir J 2002;20:185s.**
14. **Mountain CF: Revisions in the international system for staging lung cancer. Chest 1997;111:1710-1717.**
15. **Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Statist Assoc 1958;53:457-481.**
16. **Cox RD: Regression models and life tables. J Roy Stat Soc B 1972;34:205-207.**

17. Jazieh AR, Hussain M, Howington JA, Spencer HJ, Husain M, Grismer JT, Read RC: Prognostic factors in patients with surgically resected stages I and II non-small cell lung cancer. Ann Thorac Surg 2000 2000;70:1168-1171.

18. Albain KS: Invited commentary to "Lung cancer in women compared with men: stage, treatment, and survival". Ann Thorac Surg 1998;66:1143-1144.

19. Ouellette D, Desbiens G, Emond C, Beauchamp G: Lung cancer in women compared with men: stage, treatment and survival. Ann Thorac Surg 1998;66:1140-1144.

20. Sorenson JB, Badsberg JH: Prognostic factors in stage I and II adenocarcinoma of the lung: a multivariate regression analysis of 137 consecutive patients. J Thorac Cardiovasc Surg 1990;99:218-226.

21. Mountain CF, Lukeman JM, Hammar SP, Chamberlain DW, Coulser DL, Victor TA, Weiland LH: Lung cancer classification: the relationship of disease extent and cell type to survival in a clinical trial population. J Surg Oncol 1987;35:147-156.

22. Martini N, Bains MS, Burt ME: Incidence of local recurrence and secondary primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120-129.

23. Wigren T, Oksanen H, Kellokump-Lehtinen P: A practical prognostic index for inoperable lung cancer. J Cancer Res Clin Oncol 1997;123:259-266.

24. Canver CC, Memoli VA, Vanderveer PL, Dingivan CA, Mentzer RM: Sex hormone receptors in non-small-cell lung cancer in human beings. J Thorac Cardiovasc Surg 1994;108:153-157.

25. Vargas SO, leslie KO, Vacek PM, Socinski MA, Weaver DL: Estrogen-receptor-related protein p29 in primary non small cell lung carcinoma: pathologic and prognostic correlations. Cancer 1998;82:1495-1500.

26. Stabile LP, Siegfried JM: Sex and gender differences in lung cancer. J Gender Specif Med 2003;1:37-48.

27. Dresler CM, Gritz ER: Women and lung cancer: potential mechanisms of greater susceptiblity to tobacco smoke; in: Buist S, Mapp CE (eds): Respiratory Diseases in Women. Sheffield, UK, ERS Journal Ltd pp 146-151.

FIGURE 1 *– Survival curves of non-small cell stage I lung cancer patients by gender, obtained through Cox regression*

TABLE 1
Patient characteristics (n = 163)

Variable	Males (n = 124)	Females (n = 39)	*p* value
Smokers – n (%)	117 (98.3)	30 (78.9)	< 0.001
Stage I	62 (50.0)	25 (64.1)	0.50
> Stage I	62 (50.0)	14 (35.9)	
Age (mean ± SD)	61.5 ± 8.1	59.3 ± 11	0.24
Hemoglobin (g/dL; mean ± SD)	13.1 ± 2.0	12.3 ± 1.4	0.02
Histology – n (%)			
Adenocarcinoma	46 (37.1)	20 (51.3)	0.21
Squamous cell	64 (51.6)	14 (35.9)	
Other[a]	14 (11.3)	5 (12.8)	
Tumor size (cm; mean ± SD)	4.7 ± 2.6	4.4 ± 2.2	0.24
Postoperative Complications – n (%)	32 (26.4)	7 (17.9)	0.28
Type of surgery – n (%)			
Pneumonectomy	30 (24.2.)	5 (12.8)	0.10
Other[b]	94 (75.8)	34 (87.2)	

[a]Included adenosquamous carcinoma, large-cell carcinoma, bronchoalveolar carcinoma

[b]Included segmentectomy, lobectomy, and bilobectomy

TABLE 2
Effects of prognostic factors on mortality rates in stage 1 non-small cell lung cancer[a]

Variable	Relative Risk	95% CI	*p* value
Gender			
Male[b]	1.0	–	–
Female	0.09	0.03 - 0.25	< 0.001
Age	1.04	1.00 - 1.08	0.061
Hemoglobin	0.70	0.59 - 0.83	0.001
Histology			
Adenocarcinoma[b]	1.0	–	–
Squamous cell	0.79	0.42 - 1.48	0.537
Other[c]	4.52	1.17 -17.4	0.066
Tumor size	1.08	0.95 – 1.23	0.295
Postoperative complications	3.43	1.71 – 6.89	0.004
Type of surgery			
Pneumonectomy[b]	1.0	–	–
Other[d]	0.91	0.46 – 1.80	0.828

[a]Cox regression; [b]Reference category; [c]Included segmentectomy, lobectomy and bilobectomy; [d]Included adenosquamous carcinoma, large-cell carcinoma and bronchoalveolar carcinoma