Lung cancer: changes in histology, gender, and age over the last 30 years in Brazil

Maria Teresa Ruiz Tsukazan1,2, Álvaro Vigo3, Vinicius Duval da Silva4, Carlos Henrique Barrios4, Jayme de Oliveira Rios1, José Antônio de Figueiredo Pinto1

ABSTRACT

Objective: To describe the trends in tumor histology, gender and age among patients with non-small cell lung cancer (NSCLC) treated with lung resection. The histology of lung cancer has changed in developed countries, and there is still little information available on the topic for developing countries. Methods: This was a retrospective study of 1,030 patients with NSCLC treated with lung resection between 1986 and 2015 at a university hospital in southern Brazil. Differences in histology, stage, and type of surgery were analyzed by gender and for three periods (1986-1995, 1996-2005, and 2006-2015). Results: Most (64.5%) of the patients were males, and the main histological types were squamous cell carcinoma (in 40.6%) and adenocarcinoma (in 44.5%). The mean age at surgery during the first period was 56.4 years for women and 58.9 years for men, compared with 62.2 for women and 64.8 for men in the third period (p < 0.001). The proportion of females increased from 26.6% in the first period to 44.1% in the third. From the first to the third period, the proportion of patients with squamous cell carcinoma decreased from 49.6% to 34.8% overall (p < 0.001), decreasing to an even greater degree (from 38.9% to 23.2%) among men. Among the NSCLC patients in our sample, females with adenocarcinoma accounted for 11.9% in the first period and 24.0% in the third period (p < 0.001). Conclusions: As has been seen in developed countries, the rates of lung cancer in females in southern Brazil have been rising over the last three decades, although they have yet to surpass those observed for males in the region. The incidence of squamous cell carcinoma has decreased in males, approaching adenocarcinoma rates, whereas adenocarcinoma has significantly increased among women.

Keywords: Lung neoplasms; Epidemiology; Histology; Adenocarcinoma; Carcinoma, non-small-cell lung; Carcinoma, squamous cell.

INTRODUCTION

Non-communicable diseases (NCDs) are responsible for more than 67% of deaths worldwide. In Brazil, cancer represents the second leading cause of NCD-related deaths and lung cancer is the leading cause of cancer-related deaths, despite strong anti-smoking policies that reduced the smoking rate by half from 1989 to 2008. According to the World Health Organization, 1.6 million deaths per year are attributable to lung cancer. It is one of the few cancers with a well-known cause—smoking. The great efforts to reduce smoking and to introduce the use of cigarette filters have changed the epidemiology of lung cancer in developed countries, with an increase in the incidence of adenocarcinoma and a decrease in that of squamous cell carcinoma, as seen in the United States, Europe, and Asia. The rising number of women with lung cancer is also notable, as are the changes in their histological profile. Changes in the histological profile of lung cancer in Latin American countries have been poorly described in the literature. Little information regarding lung cancer histology, gender difference, and trends is available for the population of Brazil. This paper aims to describe and improve understanding of the epidemiology of lung cancer, including histology, gender distribution, patient age, and stage of the disease, in southern Brazil over the last 30 years.

METHODS

From records on file in the prospective surgery database of the Thoracic Surgery Division of the Hospital São Lucas, in the city of Porto Alegre, Brazil, we selected all patients with primary non-small cell lung cancer who were treated with anatomical resection between 1986 and 2015. We reviewed the pathology reports and charts of 1,062 patients. Thirty-two records were excluded because of missing data related to patient gender, patient age at surgery, type of resection, histology, and staging classification. Therefore, the final sample comprised 1,030 patients. Information about smoking was available in less than 37% of the charts, and that variable was therefore disregarded. All histological diagnoses were made by the same pathology group, and all staging was updated according to the 7th edition of the International Association for the Study of Lung Cancer classification system.
Patients with different clinical characteristics (in terms of histology, stage, and type of surgery) were analyzed by gender and for three different periods (1986-1995, 1996-2005, and 2006-2015). Proportions were compared by Pearson’s chi-square test or Fisher’s exact test. Two-way ANOVA was used in order to compare the mean age of the patients by gender and period. Means were compared by using adjusted least squares means and the Tukey-Kramer test. All analyses were performed using the Statistical Analysis System software, version 9.4 (SAS Institute, Cary, NC, USA), and the level of significance was set at 5%.

The study was approved by the Research Ethics Committee of the Hospital São Lucas of the Pontifícia Universidade Católica do Rio Grande do Sul. Because of the retrospective nature of the study, the requirement for consent was waived.

**RESULTS**

A total of 1,062 patients underwent lung resection for primary lung cancer at the Hospital São Lucas in the last 30 years, and 1,030 met the criteria for inclusion in this analysis. Of those 1,030 patients, 665 (64.5%) were male. The overall mean age at surgery was 62.8 years for the men and 60.8 years for the women. Table 1 shows the clinical characteristics of the patients, overall and by gender. Overall, the predominant histological type was adenocarcinoma (44.5%), followed by squamous cell carcinoma (40.6%). The histological types differed by gender (p < 0.001), squamous cell carcinoma being more common in men than in women (with a prevalence of 46.9% and 29.0%, respectively), whereas the opposite was found for adenocarcinoma (which had a prevalence of 40.4% and 51.8% among men and women, respectively). Differences between genders were also observed for the degree of tumor invasion (p < 0.001), lymph node classification (p < 0.023), and staging (p < 0.001), suggesting that the disease was more advanced in the men than in the women (Table 1).

According to two-way ANOVA, there was no evidence of an interaction between gender and period, suggesting that the mean age did not differ between men and women in any of the three periods studied (Figure 1). However, regardless of the period, the adjusted least squares mean ages at surgery were 62.4 and 59.7 years for men and women, respectively, approximately

| Table 1. Clinical characteristics of the patients, in the sample as a whole and by gender. |
|------------------------------------------|-----------------|-----------------|-----------------|
| Characteristic                          | Total (N = 1,030) | Male (n = 665) | Female (n = 365) | p     |
|------------------------------------------|-------------------|-----------------|-----------------|-------|
| **Histological type**                   |                   |                 |                 | < 0.001 |
| Squamous cell carcinoma                 | 418 (40.6)        | 312 (46.9)      | 106 (29)        |       |
| Adenocarcinoma                          | 458 (44.5)        | 269 (40.4)      | 189 (51.8)      |       |
| Carcinoid tumor                         | 36 (3.5)          | 15 (2.3)        | 21 (5.8)        |       |
| Large-cell carcinoma                    | 32 (3.1)          | 19 (2.9)        | 13 (3.6)        |       |
| Mucoepidermoid carcinoma                | 7 (0.7)           | 3 (0.4)         | 4 (1.1)         |       |
| Adenosquamous carcinoma                 | 49 (4.8)          | 31 (4.7)        | 18 (4.9)        |       |
| Undifferentiated NSCLC                   | 11 (1.0)          | 7 (1.0)         | 4 (1.1)         |       |
| Other                                    | 19 (1.8)          | 9 (1.4)         | 10 (2.7)        |       |
| **Degree of tumor invasion**            |                   |                 |                 | < 0.001 |
| T1a                                      | 144 (14)          | 73 (11)         | 71 (19.5)       |       |
| T1b                                      | 109 (10.6)        | 71 (10.7)       | 38 (10.4)       |       |
| T2a                                      | 340 (33)          | 191 (28.7)      | 149 (40.8)      |       |
| T2b                                      | 152 (14.8)        | 107 (16.1)      | 45 (12.3)       |       |
| T3                                       | 237 (23.0)        | 183 (27.5)      | 54 (14.8)       |       |
| T4                                       | 48 (4.6)          | 40 (6.0)        | 8 (2.2)         |       |
| **Lymph node involvement**              |                   |                 |                 | < 0.023 |
| N0                                       | 654 (63.5)        | 410 (61.6)      | 244 (66.9)      |       |
| N1                                       | 197 (19.1)        | 145 (21.8)      | 52 (14.2)       |       |
| N2                                       | 174 (16.9)        | 107 (16.1)      | 67 (18.4)       |       |
| N3                                       | 5 (0.5)           | 3 (0.5)         | 2 (0.5)         |       |
| **Stage**                                |                   |                 |                 | < 0.001 |
| IA                                       | 188 (18.3)        | 106 (15.9)      | 82 (22.5)       |       |
| IB                                       | 225 (21.8)        | 124 (18.7)      | 101 (27.7)      |       |
| IIA                                      | 147 (14.3)        | 102 (15.3)      | 45 (12.3)       |       |
| IIB                                      | 175 (17.0)        | 131 (19.7)      | 44 (12.0)       |       |
| IIIA                                     | 237 (23.0)        | 157 (23.6)      | 80 (21.9)       |       |
| IIIIB                                     | 21 (2.0)          | 16 (2.4)        | 5 (1.4)         |       |
| IV                                        | 37 (3.6)          | 29 (4.4)        | 8 (2.2)         |       |

NSCLC: non-small cell lung cancer. "Values expressed as n (%).
2.7 years higher for men (p < 0.001). Similarly, regardless of gender, the adjusted least squares mean ages were 57.7 years for the 1986-1995 period, 62.1 years for the 1996-2005 period, and 63.4 years for the 2006-2015 period, translating to an increase of approximately 5.7 years from the first period to the last (p < 0.001).

As can be seen in Table 2, there were significant differences among the three periods in terms of the histological type (p < 0.001), especially for squamous cell carcinoma, the prevalence of which declined from 49.6% in the 1986-1995 period to 43.0% in the 1996-2005 period and to 34.8% in the 2006-2015 period. However, in those same periods, the prevalence of adenocarcinoma increased from 38.1% to 41.2% and 49.5%, respectively. The most common type of surgery was lobectomy, which was performed in 72.5% of cases in the first period, compared with 83.6% in the third period (p < 0.001). The proportion of cases in which pneumonectomy was performed trended down, from 19.7% in the first period to 9.7% in the third period, as did that in which bilobectomy was performed, from 7.8% in the first period to 4.1% in the third period. There was also a significant difference among the periods in terms of the staging (p < 0.001), with an increase in the proportion of cases classified as stage I.

The distribution of histological types was determined by gender and period (Figure 2). In the 2006-2015 period, squamous cell carcinoma and adenocarcinoma were the main histological types among men, whereas adenocarcinoma was the predominant histological type among women. Overall, the prevalence of adenocarcinoma increased from 38.1% to 41.2% and 49.5% in the 1986-1995 period, 1996-2005 period, and 2006-2015 period, whereas that of squamous cell carcinoma decreased from 49.6% to 43.0% and 34.8%, respectively. Overall, squamous cell carcinoma was the most common histological type among men, although its prevalence declined from 38.9% in the 1986-1995 period to 23.2% in the 2006-2015 period, being equal to that of adenocarcinoma in the latter. Although the proportion of women with lung cancer was lower than that of men with lung cancer in all three periods, the prevalence of adenocarcinoma among women seems to be increasing over time. Other histological types were less common in both genders and did not show an apparent trend over the study period.

**DISCUSSION**

In southern Brazil, the characteristics of lung cancer have changed over the past 30 years. The increase
in the mean age at surgery could be indicative of the aging of the lung cancer patient population, not only at diagnosis but also eligible patients for surgical treatment. Other chronic diseases are now better controlled, leading to an increase in life expectancy and allowing enough time for lung cancer to develop. When compared with that reported for developed nations, the mean patient age at surgery was rather low in the present study, even if we consider only the most recent period, when the mean age was 62.8 years, compared with the 71 years reported for the United States in the Surveillance, Epidemiology and End Results data for the 2004-2008 period.\(^\text{(23)}\)

As has been seen in developed countries,\(^\text{(9,13,24)}\) our data indicate that the rates of lung cancer in females have risen over the last three decades but have yet to surpass those observed for males. That could be related to the fact that, in historical terms, women took up the practice of smoking later than did men, as well as being related to the latency period. Women started smoking in the 1950s and 1960s, which was also when filters began to be added to cigarettes because of the link found between lung cancer and smoking. During that same period, the tar content was also a concern and the tobacco industry was forced to reduce the levels of tar in cigarettes. Those factors could explain the higher incidence of adenocarcinoma in women.

The observed increase in the incidence of adenocarcinoma and decrease in that of the squamous cell subtype are in accordance with findings reported for developed countries, such as the United States, Japan, and western European countries.\(^\text{(9,13,24)}\) In contrast, a study performed in northern India showed no changes in the histology of lung cancer over the past three decades.\(^\text{(25)}\) The diagnosis of adenocarcinoma is currently extremely important, because it is more frequently associated with particular molecular abnormalities (epidermal growth factor receptor mutations and anaplastic lymphoma kinase fusions), and international guidelines recommend routine testing of adenocarcinoma patients. Current practice requires having the necessary information available in order to make the most appropriate therapeutic recommendation.

The significant decrease in pneumonectomy rates observed in the present study reflects changes in surgical management techniques and treatment indications. The decrease in the incidence of squamous cell carcinoma is directly related to a lower prevalence of central lesions requiring pneumonectomy.\(^\text{(23)}\) In addition, the use of sleeve resection allows part of the lung to be spared.

The observed decrease in the incidence of squamous cell lung cancer in Brazil is believed to be attributable to the decline in the number of smokers since 1960, as well as to the increased availability of low-tar and filter-tipped cigarettes, as also occurred in developed countries.\(^\text{(9)}\) That is probably due to the inability of filters to eliminate small particles and to the fact that the smoker tends to increase the time inhaling in order to compensate for the smaller amount of smoke passing through the filter. The immediate consequence is greater deposition of the smaller carcinogens in the periphery, the most common site for adenocarcinoma.\(^\text{(6,9)}\) The reported increase in the incidence of adenocarcinoma only among smokers supports that theory. In addition, one multicenter study demonstrated that smokers of filter-tipped cigarettes are at a lower risk of developing squamous cell carcinoma than are smokers of unfiltered cigarettes, although the risk for adenocarcinoma did not differ between the two groups.\(^\text{(13)}\)

It is well known that observational analyses based on clinical data have methodological limitations,\(^\text{(26)}\) such as the lack of information regarding smoking status or other important clinical variables. Nevertheless, we believe that our findings are relevant. They provide a description of the histological profile of lung cancer in one state in southern Brazil, which has had a higher incidence of lung cancer over the last 30 years than any other state in the country. Whether or not our results can be generalized to other states in Brazil is a subject for further research. One strength of our study is that all of the slides were analyzed by the same pathology group, according to the most recent staging classification system, and that the surgical team remained uniform throughout the study period.

In summary, there were significant changes in the epidemiology of lung cancer in southern Brazil over the past three decades. The incidence of lung cancer among women in the region has increased. Adenocarcinoma has become the most common histological type, especially among women, and the mean age of patients eligible for lung cancer resection has increased for both genders.

**ACKNOWLEDGMENTS**

The authors want to thank the Hospital São Lucas of the Pontifícia Universidade Católica do Rio Grande do Sul, especially the Pathology Department, and the Universidade Federal do Rio Grande do Sul, for providing access to information and for supporting this project.
REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: WHO; c2016 [cited 2017 Apr 9]. Global status report on noncommunicable diseases 2014 [about 2 screens]. Available from: http://www.who.int/nmh/publications/ncd-status-report-2014/en/

2. Schmidt MJ, Duncan BB, Azevedo e Silva GA, Menezes AM, Monteiro CA, Barreto SM, et al. Chronic non-communicable diseases in Brazil: burden and current challenges. Lancet. 2011;377(9781):1949-61. https://doi.org/10.1016/S0140-6736(11)60135-9

3. Levy D, de Almeida LM, Szlko A. The Brazil SimSmoke policy simulation model: the effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation. PLoS Med. 2012;9(11):e1001336. https://doi.org/10.1371/journal.pmed.1001336

4. World Health Organization; International Agency for Research on Cancer (IARC) [homepage on the Internet]. Lyon: IARC; c2016 [cited 2017 Apr 9]. World Cancer Report 2014 [about 2 screens]. Available from: http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014

5. Shopland DR, Eyre HJ, Pechacek TF. Smoking-attributable cancer mortality in 1991: is lung cancer now the leading cause of death among smokers in the United States? J Natl Cancer Inst. 1991;83(16):1142-8. https://doi.org/10.1093/jnci/83.16.1142

6. Osann KE. Epidemiology of lung cancer. Curr Opin Pulm Med. 1998;4(4):198-204. https://doi.org/10.1097/00063198-199807000-00002

7. Chen K, Wang PP, Sun B, Li Q, Perruccio A, Power D, et al. Twenty-year secular changes in sex specific lung cancer incidence rates in an urban Chinese population. Lung Cancer. 2006;51(1):13-9. https://doi.org/10.1016/j.lungcan.2005.08.013

8. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. J Clin Oncol. 2005;23(14):3175-85. https://doi.org/10.1200/JCO.2005.10.462

9. Janssen-Heijnen ML, Coebergh JW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. Lung Cancer. 2001;31(2-3):123-37. https://doi.org/10.1016/S0169-5002(00)00197-5

10. Charloux A, Quoix E, Wolkove N, Small D, Pauli G, Kreisman H. The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. Int J Epidemiol. 1997;26(1):14-23. https://doi.org/10.1093/ije/26.1.14

11. Janssen-Heijnen ML, Coebergh JW. The changing epidemiology of lung cancer in Europe. Lung Cancer. 2003;41(3):245-58. https://doi.org/10.1016/S0169-5002(03)00230-7

12. Chang JVV, Asamura H, Kawachi R, Watanabe S. Gender difference in survival of resected non-small cell lung cancer: histology-related phenomenon? J Thorac Cardiovasc Surg. 2009;137(4):807-12. https://doi.org/10.1016/j.jtcs.2008.09.026

13. Patel JD. Lung cancer in women. J Clin Oncol. 2005;23(14):3212-8. https://doi.org/10.1200/JCO.2005.11.488

14. Tan YK, Wee TC, Koh WP, Wang YT, Eng P, Tan WC, et al. Survival among Chinese women with lung cancer in Singapore: a comparison by stage, histology and smoking status. Lung Cancer. 2003;40(3):237-46. https://doi.org/10.1016/S0169-5002(03)00038-2

15. Rivera MP, Stover DE. Gender and lung cancer. Clin Chest Med. 2004;25(2):391-400. https://doi.org/10.1016/j.ccm.2004.01.006

16. Xie L, Ugnat AM, Morris J, Semenciw R, Mao Y. Histology-related variation in the treatment and survival of patients with lung carcinoma in Canada. Lung Cancer. 2003;42(2):127-39. https://doi.org/10.1016/S0169-5002(03)00283-6

17. Little AG, Gay EG, Gaspar LE, Stewart AK. National survey of non-small cell lung cancer in the United States: epidemiology, pathology and patterns of care. Lung Cancer. 2007;57(3):253-60. https://doi.org/10.1016/j.lungcan.2007.03.012

18. Caldarella A, Crocetti E, Comin CE, Janni A, Pega AL, Paci E. Gender differences in non-small cell lung cancer: a population-based study. Eur J Surg Oncol. 2007;33(8):763-8. https://doi.org/10.1016/j.ejso.2007.01.001

19. Novais FT, Cataneo DC, Ruiz Junior RL, Defaveri J, Michelin OC, Cataneo AJ. Lung cancer: histology, staging, treatment and survival. J Bras Pneumol. 2008;34(8):595-600. https://doi.org/10.1590/S1806-37132008000800009

20. Goldstraw P. New TNM classification: achievements and hurdles. Transl Lung Cancer Res. 2013;2(4):264-72.

21. Goldstraw P. Updated staging system for lung cancer. Surg Oncol Clin N Am. 2011;20(4):655-66. https://doi.org/10.1016/j.soc.2011.07.005

22. Travis WD. Pathology of lung cancer. Clin Chest Med. 2011;32(4):605-44. https://doi.org/10.1016/j.ccm.2011.08.005

23. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011;32(4):669-44. https://doi.org/10.1016/j.ccm.2011.09.001

24. Hammond EC, Selikoff IJ, Lawther PL, Seidman H. Inhalation of benzpyrene and cancer in man. Ann N Y Acad Sci. 1976;271:116-24. https://doi.org/10.1111/j.1749-6632.1976.tb23100.x

25. Hammoud EC, Selikoff IJ, Lawther PL, Seidman H. Inhalation of benzpyrene and cancer in man. Ann N Y Acad Sci. 1976;271:116-24. https://doi.org/10.1111/j.1749-6632.1976.tb23100.x

26. Schottenfeld D. The etiology and epidemiology of lung cancer. In: Pass HI, Carbone DP, Johnson DH, Minna JD, Scagliotti GV, editors. Principles and Practice of Lung Cancer. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010. p.3-22.

27. Overhage JM, Overhage JM. Sensible use of observational clinical data. Stat Methods Med Res. 2013;22(1):7-13. https://doi.org/10.1177/0962280211403598