



ORIGINAL RESEARCH PAPER

Medicine

ROLE OF SMOKING STATUS ON LONG-TERM SURVIVAL IN PATIENTS OPERATED FOR NON-SMALL CELL LUNG CANCER

KEY WORDS: Non-small cell lung cancer, tobacco smoking, survival

Kumbasar U*	Hacettepe University Faculty of Medicine, Department of Thoracic Surgery 06100, Sıhhiye, Ankara, Turkey*Corresponding Author
Uysal S	Hacettepe University Faculty of Medicine, Department of Thoracic Surgery 06100, Sıhhiye, Ankara, Turkey
Dikmen E	Hacettepe University Faculty of Medicine, Department of Thoracic Surgery 06100, Sıhhiye, Ankara, Turkey
Demircin M	Hacettepe University Faculty of Medicine, Department of Thoracic Surgery 06100, Sıhhiye, Ankara, Turkey
Dogan R	Hacettepe University Faculty of Medicine, Department of Thoracic Surgery 06100, Sıhhiye, Ankara, Turkey

ABSTRACT

Although tobacco smoking is one of the major causes of lung cancer the correlation between smoking status and the survival of patients is uncertain. **Aims:** This present study aimed to evaluate both the frequency of non-smoking patients and the impact of smoking status to the long-term survival of patients operated for NSCLC in our institutional cohort. **Methods:** Medical records of 249 patients who underwent pulmonary resection for NSCLC were retrospectively reviewed. Patients were divided into smokers and never-smokers. Annual frequency, demographic and clinical characteristics and overall survival were compared between the groups. **Results:** The annual frequency of never-smokers between the years 2002 and 2012 was 33.2, 24, 37.5, 25, 34.3, 35.4, 29.4, 22.7, 22.2, 35.7 and 28.5%, respectively. There were no statistically significant difference in terms of the distribution of age (p=0.993), FEV1 measurement (p=0.476), type of resection performed (p=0.564) and tumor histology (p=0.920) between the groups. The median survival time was similar in both groups (72 vs 76 months, smokers vs. never-smokers. Log-rank test; P=0.654). **Conclusion:** The proportion of never-smokers were approximately 30% in our cohort. In long follow-up, smoking status was not an independent risk factor for a poorer prognosis in patients operated for NSCLC.

INTRODUCTION

Lung cancer is the leading cause of cancer related death worldwide, accounting for about 1.6 million deaths per year . Although there is clear association between tobacco smoking and non-small cell lung cancer (NSCLC), 10 – 15% of all lung cancers arise in never smokers . In addition, many studies showed that the incidence of lung cancer in never-smokers is increasing globally . There is also little information available about the impact of smoking status on the survival of patients with NSCLC, and the results of the studies are conflicting .

In this present study, we aimed to evaluate both the frequency of non-smoking patients and the impact of smoking status to the long-term survival of patients operated for NSCLC in our institutional cohort.

Materials and Methods

Between January, 2002 and December, 2012, 249 patients who underwent complete pulmonary resection for NSCLC at our institutions were retrospectively analyzed from a prospectively collected database. The study was approved by the ethical committee of Hacettepe University Medical Faculty. Survival status was determined from the date of last follow-up. Mortality status was documented from patient records and the National Health Service database.

Patients' data were collected including the following variables: sex, age, forced expiratory volume in the first second (FEV1), tumour histologic subtype, type of resection, preoperative comorbidities and postoperative early complication. Never-smokers were defined as patients who did not ever smoke any tobacco in their lifetimes. Smokers were defined as patients who continued smoking upon diagnosis or had stopped smoking at least one month before admission for operation and had smoked more than 100 cigarettes during their lifetimes. Preoperative comorbidities included hypertension, diabetes mellitus, coronary artery disease and chronic obstructive pulmonary disease. Postoperative early complications were defined as prolonged air leak, postoperative

ventilatory support, rhythm disturbances and surgical site infections. Patients were divided into smokers and never-smokers. Annual frequency, demographic and clinical characteristics and overall survival were compared between the groups.

Statistical analysis

Statistical analyses were performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean±std. deviation, categorical variables as frequency and percent. Continuous variables were compared with the independent sample t test or Mann-Whitney U test for two groups. Categorical variables were compared using Chi-square test. Survival was estimated by using the Kaplan-Meier method. Survival distribution was compared by log-rank test. P value of less than 0.05 was considered statistically significant for all tests.

Results

Of the 249 patients included, 208 (83.5%) were male and 41 (16.5%) were female. The median age at admission was 60.8 years (range, 35 to 81). Among them, 75 patients (30.1%) were never-smokers. The patient characteristics are summarized in Table 1. The annual frequency of never-smokers between the years 2002 and 2012 was 33.2, 24, 37.5, 25, 34.3, 35.4, 29.4, 22.7, 22.2, 35.7 and 28.5%, respectively (Figure 1). Never smokers were more likely to be female 46.3% vs 26.9% male (P=0.022). No statistically significant difference existed in the distribution of age (p=0.993), FEV1 measurement (p=0.476), type of resection performed (p=0.564) and tumor histology (p=0.920) between the groups (Table 2).

Table 1. The patient characteristics.

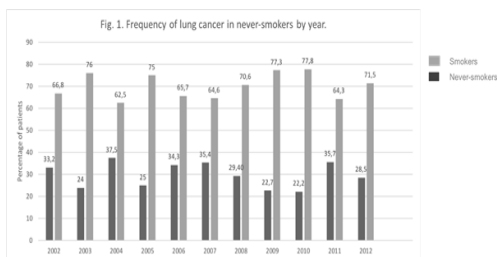
Variable	Mean (SD) (Minimum-maximum)
Age (years)	60.8 (9.1) (35-81)
Male (%)	208 (83.5)
FEV1 (l)	2.39 (0.6) (1.1-3.9)

Preoperative comorbidity (%)	132 (53.0)
Type of operation	
Pneumonectomy (%)	66 (26.6)
Lobectomy (%)	177 (71.0)
Segmentectomy (%)	6 (2.4)
Tumor histology	
Adenocarcinoma	93 (37.3)
Squamous cell carcinoma	114 (45.8)
Large-cell carcinoma	21 (8.4)
Other	21 (8.4)
Postoperative complications	156 (62.6)
Hospital stay (days)	9.9 (7.9) (4-60)

Table 2. Baseline characteristics of the study population.

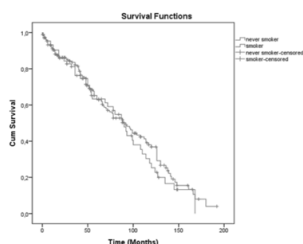
Variable	Smoker (n=174)	Non-smoker (n=75)	P value
Age (years) (SD)	60.82±9.2	60.83±9.0	0.993
Gender (%)			0.022
Female	22 (12.6)	19 (25.3)	
Male	152 (87.4)	56 (74.7)	
FEV1 (l)	2.38±0.68	2.41±0.6	0.476
Type of resection (%)			0.564
Pneumonectomy	55 (25.8)	21 (26)	
Lobectomy	125 (71.9)	52 (69.3)	
Segmentectomy	4 (2.3)	2 (2.7)	
Postoperative complication (%)	72 (41.4)	25 (33.3)	0.232
Tumor histology (%)			0.920
Adenocarcinoma	65 (37.4)	28 (37.3)	
Squamous-cell carcinoma	77 (44.3)	37 (49.3)	
Large-cell carcinoma	16 (9.2)	5 (6.7)	
Mixt	8 (4.6)	2 (2.7)	
Other	8 (4.6)	3 (4)	

Figure 1. Frequency of lung cancer in never-smokers by years.



Out of 249 patients, 146 (%58.6) died and 103 (41.4%) survived during the study period. The median survival time was 72 months in smokers and 76 months in never-smokers (log-rank test; P=0.654). The Kaplan–Meier estimates of the overall survival functions of the groups are shown in Figure 2.

Figure 2. Overall survival of patients with non-small cell lung cancer according to smoking status.



DISCUSSION

Lung cancer is classified as a preventable cancer since tobacco smoking is considered to be the major cause of lung cancer. Although there is a decline in the incidence of lung cancer the question whether the number of never-smoking patients with NSCLC is increasing is very difficult to address due to poorly recorded smoking histories in the past and demographic factors which may affect the actual percentage of the population (9). However, vast amount of studies highlighted an increase in the proportion of never-smoking patients with NSCLC (3, 10, 11).

According to global statistics, the proportion of never-smokers among NSCLC patients is around 10%-15% in Western countries and approximately 32% in Asian region (12, 13). In our cohort the proportion of never-smoker patients undergoing surgery for lung cancer was 30.1% which is parallel to Asian population and we also pointed out that the annual percentage did not change considerably in the 10 years' period. This latter conflicting observation may be explained by demographic diversity and the lack of previous data regarding this issue.

NSCLC in newer smokers could be described as a distinct disease due to its differences from NSCLC in ever-smokers in terms of epidemiologic, clinical, molecular characteristics and high occurrence in women population and with adenocarcinoma histology (10, 13). In our study, proportion of female patients among non-smokers were higher which is in line with the previous studies. However, the major histologic type in the never-smoker group was squamous cell carcinoma which is inconsistent with the literature.

There is a debate whether smoking status at the time of diagnosis has an impact on overall survival of patients with lung cancer (14, 15). Some studies described smoking as a predictor of poor prognosis in patients with lung cancer (7, 8, 16, 17). Recently, Cho et al. analysed 1860 patients who were newly diagnosed with NSCLC in Korea and emphasised that never-smoker patients had a longer overall survival compared with ever-smokers due to their different clinical characteristics and major driver mutations (11). More recently, Cufari et al. reported that the 5-year survival was lower for ex-smokers than never-smokers in patients operated for NSCLC at a tertiary care hospital in the United Kingdom (3). In contrast, other studies reported no difference in survival between ever-smokers and never-smokers and putted forward smoking status as an insignificant prognostic factor (6, 18, 19). Correspondingly, the results of our study demonstrate similar overall survival among never-smokers compared to smokers (median survival 76 and 72 months, respectively; P=0.654).

This study had limitations that should be addressed. First of all, it is a retrospective study and cause specific mortality could not be evaluated. Secondly, the sample size was relatively small. Thirdly, information about exposure to other risk factors and passive cigarette smoking status was unavailable. We also acknowledge that our observations are limited with a single institution. However, as our institution is a large volume tertiary institution for lung cancer resections, we think that we have a considerable proportion of the cross-sectional cohort for NSCLC patients in Turkey.

To sum up, according to our study, virtually 30% of Turkish patients operated for NSCLC were never-smokers. This percentage remains reasonably stable between the years 2002 and 2012. In long follow-up, never-smokers had similar survival rates compared to smokers. However, our data deserve further verification with multi-centre and larger scale prospective trials.

REFERENCES

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
- Thun MJ, Henley SJ, Burns D, Jemal A, Shanks TG, Calle EE. Lung cancer death rates in lifelong nonsmokers. J Natl Cancer Inst. 2006;98(10):691-9.
- Cufari ME, Proli C, De Sousa P, Raubenheimer H, Al Sahaf M, Chavan H, et al. Increasing frequency of non-smoking lung cancer: Presentation of patients with early disease to a tertiary institution in the UK. European journal of cancer. 2017;84:55-9.
- Davis DL. Trends in nonsmoking lung cancer. Epidemiology. 1993;4(6):489-92.
- Lee SJ, Lee J, Park YS, Lee CH, Lee SM, Yim JJ, et al. Impact of smoking on mortality

- of patients with non-small cell lung cancer. *Thorac Cancer*. 2014;5(1):43-9.
6. Meguid RA, Hooker CM, Harris J, Xu L, Westra WH, Sherwood JT, et al. Long-term survival outcomes by smoking status in surgical and nonsurgical patients with non-small cell lung cancer: comparing never smokers and current smokers. *Chest*. 2010;138(3):500-9.
 7. Ferketich AK, Niland JC, Mamet R, Zornosa C, D'Amico TA, Ettinger DS, et al. Smoking status and survival in the national comprehensive cancer network non-small cell lung cancer cohort. *Cancer*. 2013;119(4):847-53.
 8. Nakamura H, Haruki T, Adachi Y, Fujioka S, Miwa K, Taniguchi Y. Smoking affects prognosis after lung cancer surgery. *Surg Today*. 2008;38(3):227-31.
 9. Pelosof L, Ahn C, Gao A, Horn L, Madrigales A, Cox J, et al. Proportion of Never-Smoker Non-Small Cell Lung Cancer Patients at Three Diverse Institutions. *J Natl Cancer Inst*. 2017;109(7).
 10. Yano T, Miura N, Takenaka T, Haro A, Okazaki H, Ohba T, et al. Never-smoking nonsmall cell lung cancer as a separate entity: clinicopathologic features and survival. *Cancer*. 2008;113(5):1012-8.
 11. Cho J, Choi SM, Lee J, Lee CH, Lee SM, Kim DW, et al. Proportion and clinical features of never-smokers with non-small cell lung cancer. *Chin J Cancer*. 2017;36(1):20.
 12. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
 13. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, Yap SP, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(15):2245-51.
 14. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *Bmj*. 2010;340:b5569.
 15. Zhou W, Heist RS, Liu G, Park S, Neuberg DS, Asomaning K, et al. Smoking cessation before diagnosis and survival in early stage non-small cell lung cancer patients. *Lung Cancer*. 2006;53(3):375-80.
 16. Nordquist LT, Simon GR, Cantor A, Alberts WM, Bepler G. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. *Chest*. 2004;126(2):347-51.
 17. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. *Chest*. 2004;125(1):27-37.
 18. Toh CK, Wong EH, Lim WT, Leong SS, Fong KW, Wee J, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: a retrospective analysis. *Chest*. 2004;126(6):1750-6.
 19. Subramanian J, Velcheti V, Gao F, Govindan R. Presentation and stage-specific outcomes of lifelong never-smokers with non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2007;2(9):827-30.