ORIGINAL ARTICLE

Prognostic factors for survival in a Chinese population presenting with advanced non-small cell lung cancer with an emphasis on smoking status: A regional, single-institution, retrospective analysis of 4552 patients

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Abstract

Background: Lung cancer ranks as the top of cancer-related mortality in the world. Approximately 85–90% of all lung cancer cases are non-small cell lung cancer (NSCLC). For advanced NSCLC patients, the five-year survival rate is less than 5%. Previous studies have attempted to determine prognostic factors, such as smoking status, gender, ethnicity, age, and histological type. However, the results are controversial and conflict. In this study, we investigated prognostic factors in a Chinese population presenting with advanced NSCLC.

Methods: Medical records of patients with advanced NSCLC (AJCC Stage IIIB/IV) who received treatment at our institution were reviewed. Kaplan-Meier method and Cox Proportional Hazards model were performed in both univariate and multivariate analyses.

Results: A total of 4552 patients were entered. Among them, 1320 (29.0%) were female, 2408 non-smokers (52.9%), and all had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) = 0/1. Univariate analysis suggested that female gender (P < 0.001), adenocarcinoma histology (P < 0.001), age <70 (P < 0.001), and non-smoker status (P < 0.001) were associated with better survival. However, multivariate analysis demonstrated that age (hazard ratio [HR] = 1.173, 95% confidence interval [CI]: 1.085–1.268, P < 0.001), smoking status (vs. non-smokers, HR = 1.212, 95% CI: 1.123–1.308, P < 0.001), and histological type (non-adenocarcinoma vs. adenocarcinoma, HR = 1.104, 95% CI: 1.031–1.181, P = 0.004), but not gender, were independent prognostic factors.

Conclusions: Smoking status, age, and histological type are independent prognostic factors in Chinese NSCLC patients presenting with advanced disease. Non-smoking status is associated with better overall survival in Chinese NSCLC patients.

Introduction

Lung cancer incidence has escalated dramatically during the past few decades. The standardized incidence ratio has increased in the Chinese population since 2000.[1] Lung cancer was also responsible for nearly 1.4 million deaths worldwide in 2008.[2] In China, it is increasing both in prevalence and mortality.[2,3] There are numerous proposed causes for its development and increasing mortality, but the primary cause remains tobacco smoking.[4,5]

Several reports have also regarded smoking as a significant prognostic factor.[6,7] Studies have shown that the clinical characteristics and prognosis of lung cancer in non-smokers are substantially different from those in smokers.[8] However, this association has not been observed in all studies.[9–11] These conflicting results may be attributed to potentially confounding

factors such as a different definition of smoking status, age, gender, and histology.

Other factors, such as gender[12,13] and histological type,[14,15] seem also to play an important role in prognosis, but not all studies have found them to be prognostic factors.[14,16]

Because of these differing results from previous studies, we conducted a retrospective study analyzing the prognostic significance of various factors in non-small cell lung cancer (NSCLC), the first such analysis in Mainland China.

Materials and methods

Patients

Patients presenting with advanced NSCLC seen between January 2002 and December 2009 at the Medical Oncology Department of Tongji University Affiliated Shanghai Pulmonary Hospital were retrospectively studied. The diagnosis was confirmed at this hospital by positive histological or cytological examinations. Patients had to have had documented information on smoking history available.

Methods

A registry database regarding demographics, smoking status, histology, and performance (PS) status according to the Eastern Cooperative Oncology Group (ECOG) scale, stage, treatment, and survival was available. Patients' demographic data included gender and age. Regarding smoking, "non-smokers" were defined as having smoked less than 100 cigarettes throughout their life-time and had not used other tobacco products. Histological types were determined according to the World Health Organization's Classification.[17] The category of mixed/carcinoma, not otherwise specified (NOS)/other, were obtained by examining specimens that did not further classify NSCLC into adenocarcinoma (ADC), squamous cell, or large cell. Disease extent was determined by TNM classification of the Sixth Edition American Joint Committee on Cancer (AJCC) Staging System.[18] Treatment was defined as an anticancer therapy received within six months of diagnosis.[19] The interval between dates of diagnosis and death or last visit was defined as survival.

Statistical analysis

Comparisons of demographic, clinical, and pathologic variables were made using the x2 method and Pearson's test. Kaplan-Meier method was used to analyze survival data, and statistical differences were evaluated by the log-rank test. Univariate and multivariate analyses were performed to test the significance of prognostic factors including gender, age, smoking status, and histology by Cox's proportional hazards

ratio model. The significance level of P-value was set at less than 0.05. The statistical software SPSS version 13.0 was used to perform all analyses.

Results

Patients

During the 7-year period, 4552 cases with NSCLC were collected, with a median age of sixty. Baseline characteristics are presented in Table 1. There were 1320 female and 3232 male patients. There were 56.1% ADCs. Of 4552 patients, 3119 [68.5%] had stage IV disease. Of the population, 84.9% received chemotherapy only. At the time of data collection, 10.7% were alive. Lost-to-follow-up was seven percent. Patient characteristics stratified by smoking status are listed in Table 2. There was a male predominance of smokers, while non-smokers were younger and had more ADCs (P < 0.001).

Univariate analysis of overall survival

Figure 1 shows survival of patients according to age, gender, smoking status, and histology, respectively. Survival differences were statistically significant in all subgroups.

Table 1 Patient characteristics

Characteristics	Patient number (%)
Overall	4552
Age, yr (median 60; range, 33–85)	
≤70	3685 (81.0%)
>70	867 (19.0%)
Gender	
Male	3232 (71.0%)
Female	1320 (29.0%)
Histological type	
Adenocarcinoma†	2555 (56.1%)
Squamous	1099 (24.1%)
Mixed/NOS/Others	898 (20.8%)
Clinical Stage	
IIIB	1433 (31.5%)
IV	3119 (68.5%)
Treatment	
Chemotherapy only	3868 (84.9%)
Chemoradiotherapy	584 (12.8%)
EGFR-TKI	100 (2.3%)
Smoking status	
Non-smoker	2408 (52.9%)
Smoker	2144 (47.1%)
Survival status	
Dead	3743 (82.3%)
Alive	491 (10.7%)
Censored	318 (7.0%)

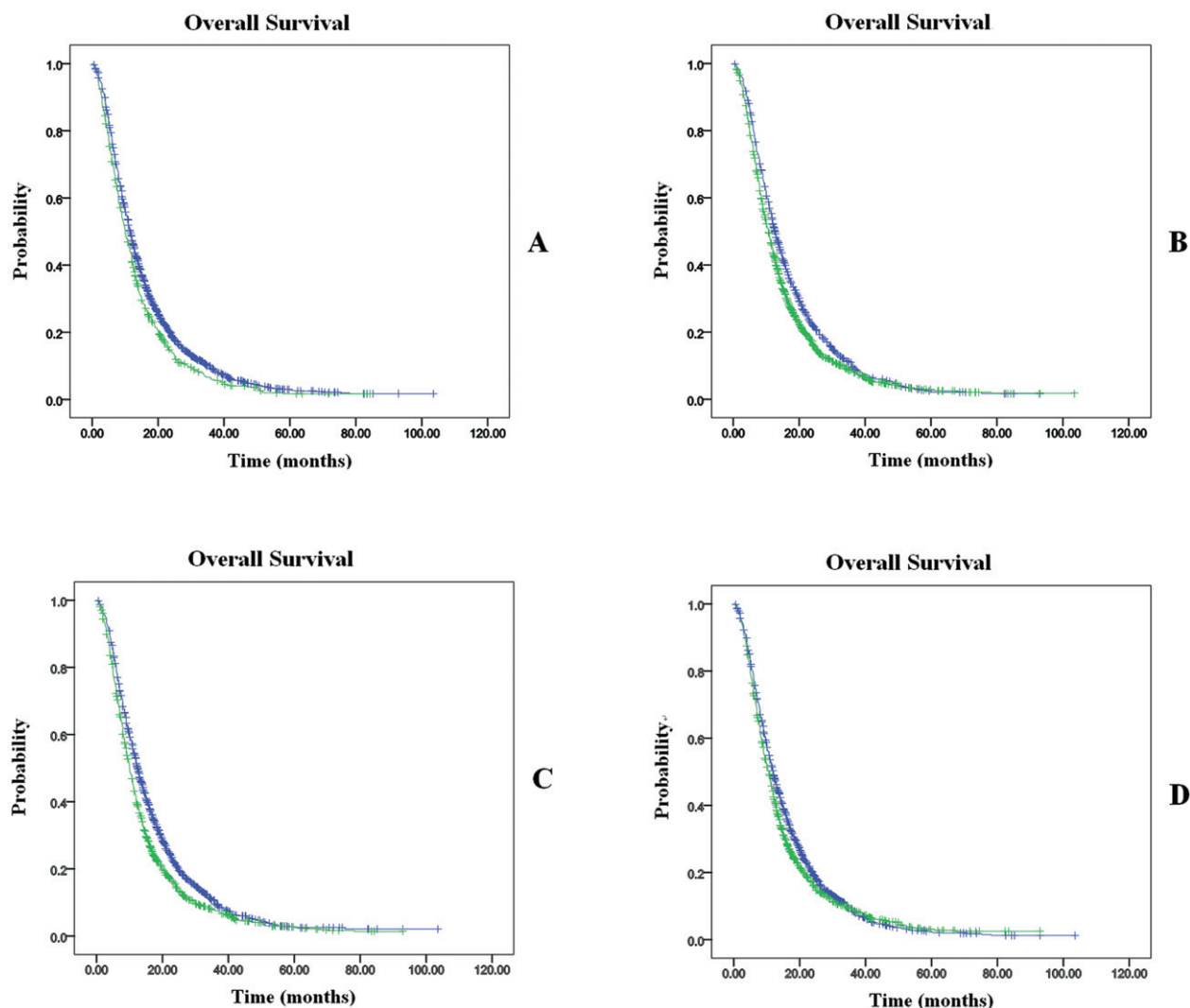†The number of female adenocarcinoma is 1052.

Figure 1 (**a–d**) show the survival curve of patients according to different stratified factors. (**a**) Patients under 70-years-old had a significant survival benefit compared with those above 70. Median survival time (MST) was 11.6 versus 10.0 months (P < 0.001). Age: ⌐, ≤70; ⌐, >70; +, censor; +, censor. (**b**) Female patients showed a longer MST of 12.7 months compared to male of 10.8 months (P < 0.001). Gender: ⌐, female; ⌐, male; +, censor; +, censor. (**c**): Patients with adenocarcinoma (ADC) enjoyed a better survival than non-ADC (MST 12.0 months vs. 10.6 months, P < 0.001). Smoking status: ⌐, non-smoker; ⌐, smoker; +, censor; +, censor. (**d**) As for smoking status, better survival preferred non-smokers (MST 12.5 months vs. 10.0 months, P < 0.001). Histology: ⌐, ADC; ⌐, non-ADC; +, censor; +, censor.

Patients under 70-years-old had a significant survival benefit compared with those above 70 (P < 0.001). Median OS was 11.6 and 10.0 months, respectively. Women had a survival benefit, with median OS of 12.7 months versus 10.8 months (P < 0.001). The survival difference was also statistically different between ADC and non-ADC (12.0 months vs. 10.6 months, P < 0.001), as well as for smokers and non-smokers (10.0 months vs. 12.5 months P < 0.001) (Table 3).

Nonsmokers in male and female subgroups had longer survival than smokers. The statistical significance was reached in male patients (non-smokers vs. smokers, 12.0 months vs. 10.0 months, P < 0.001). In female nonsmokers, we also observed a better overall survival compared with smokers (non-smokers vs. smokers, 12.9 months vs. 10.0 months, P = 0.012). There was no significant survival difference between male and female non-smokers (male vs. female, 12.0 months vs. 12.9 months, P = 0.065). Younger nonsmokers had a longer survival rate (≤70 vs. >70, 12.8 months vs.11.7 months, P = 0.008) (Table 4).

Multivariate analysis of overall survival

Cox analysis of the 4552 patients showed that non-smoker status was a significant favorable prognostic factor, as well as

Table 2 Correlation between smoking history and clinico-pathological characteristics

Smoking history, number of patients (%)			
Characteristics	Non-smoker	Smoker	*P* value
Total	2408 (52.9%)	2144 (47.1%)	
Age			
≤70	2014 (83.6%)	1671 (77.9%)	<0.001*
>70	394 (16.4%)	473 (22.1%)	
Gender			
Male	1137 (47.2%)	2095 (97.7%)	<0.001*
Female	1271 (52.8%)	49 (2.3%)	
Histology			
Adenocarcinoma	1653 (68.6%)	906 (42.1%)	<0.001*
Non-adenocarcinoma	755 (31.4%)	1242 (57.9%)	

*Indicates significance.

Table 4 Univariate Analyses of Prognostic Factors in different subsets

Factors	Overall Survival (months)	P value
Male		
Non-smokers	12.0	<0.001*
Smokers	10.0	
Female		
Non-smokers	12.9	0.012
Smokers	10.0	
Non-smokers		
Male	12.0	0.065
Female	12.9	
Non-smoker		
≤70	12.8	0.008*
>70	11.7	

*Indicates significance.

was younger age and ADC histology (Table 5). However, gender was no longer an independent prognostic factor. (Table 5)

Discussion

Many prognostic factors have been shown to be related to NSCLC, including disease extent, performance status, weight loss, smoking status, ethnicity, and gender.[20–22] A patient's smoking status remains the predominant impact on prognosis in NSCLC. One study demonstrated that non-smokers had a significantly better survival compared with smokers (18.5 months vs. 13.6 months), although surprisingly this did not reach statistical significance.[23] This may be due to patients' performance status, which included patients with ECOG 2–4, while in the present study patients were, ECOG PS 0–1. Also, our study did not include a former smoker group. Although several studies demonstrated smoking to be an independent and significant prognostic factor of

Table 3 Univariate analyses of prognostic factors

Factors	Overall Survival (months)	*P* value
Overall	11.2	
Age		
≤70	11.6	<0.001*
>70	10.0	
Gender		
Male	10.8	<0.001*
Female	12.7	
Smoking history		
Non-smokers	12.5	<0.001*
Smokers	10.0	
Histological type		
Adenocarcinoma	12.0	<0.001*
Non-adenocarcinoma	10.6	

*Indicates significance.

NSCLC,[14,24–26] not all studies agreed with smoking status being a prognostic factor.[22,27,28] Table 6 describes such studies. Different study populations and different stratification factors[22,28] may have contributed to the differing results. Thus, we conducted this study to further investigate prognostic factors for their survival in NSCLC. Furthermore, there is no previous study of such a Chinese population in Mainland China.

In univariate analysis, younger age, female gender, ADC, and smoking status (Table 3) were found to be associated with better OS. The overall survival of smokers and non-smokers was 10.0 months and 12.5 months, respectively (P < 0.001). However, female gender was excluded as an independent prognostic factor by multivariate analysis. This result is not consistent with a meta-analysis, which considered female gender as an independent prognostic factor in NSCLC.[29] However, among 39 studies included in this meta-analysis, only three studies were focused on advanced NSCLC. Furthermore, of these three studies, only one study found significant prognostic differences between male and female. The rest of studies selected for the meta-analysis recruited patients with early stage NSCLC, most resectable, as it is known to all that operable NSCLC are highly curable. Therefore, the favorable prognostic outcomes in females demonstrated by this meta-analysis may be ascribed to the stage. The result of multivariate analysis, which regarded female gender as a prognostic factor independent of smoking status, may be a little difficult, because only 1/3 of the studies listed in the meta-analysis were used. Notably, there was no illustration of smoking status of all studies included in the meta-analysis. We further performed a comparison between non-smokers and smokers when stratified by gender (Fig 2) and demonstrated no statistical significance in OS between male non-smokers and female non-smokers (12.0 mos vs. 12.9 mos, P = 0.065). Furthermore, we observed an improvement of OS in non-smokers, both male and female (Table 5). Since there were many more non-smokers compared with smokers

Table 5 Multivariate analyses of prognostic factors

Factors	Unfavorable	Favorable	HR	95% CI	P value
Age (yr)	≥70	<70	1.173	1.085–1.268	<0.001*
Gender	Male	Female	1.070	0.983–1.165	0.116
Smoking history	Smoker	Non-smoker	1.212	1.123–1.308	<0.001*
Histological type	Non-adenocarcinoma	Adenocarcinoma	1.104	1.031–1.181	0.004*

*Indicates significance. CI, confidence interval; HR, hazard ratio for death.

in females (51 female smokers compared with 1271 non-smokers), the differing results in men versus women may be ascribed to the number of smokers. We also found that non-smokers were more likely to be women, younger, and to have ADC, in agreement with other reports.[8,22,30] Therefore, it seems plausible that the prognostic benefit in females is accounted for the improved survival in the non-smoker subset, rather than gender.

Age, as well as smoking status, is an independent prognostic factor. Interestingly, in age subsets (Table 3), we observed a significant difference between smokers and non-smokers. This may be partly explained by the fact that co-morbidities such as cardiovascular and chronic obstructive disease increase with age,[31] especially in smokers, thus also affecting prognosis. We also found a significant difference between age subsets in non-smokers (Fig 3). This result can be explained through a recent retrospective study indicating that elderly patients receive less aggressive treatment,[32] which may contribute to their shortened OS.

Table 6 Studies of NSCLC on smoking status and prognosis

Author	Year	Stratified factors	P
Studies without a difference			
Toh, CK, *et al.*	2004[27]	Non-smoker Smoker	0.923
Tsao AS, et. al.	2005[28]	Never-smoker Former smoker Current smoker	0.5
Ayesha, et.al.	2007[22]	Current smoker Smoker Non-smoker	0.07
Takeshi, *et al.*	2008[23]	Former smoker Never smoker	0.871
Studies with a difference			
Itaya T, *et al.*	2007[14]	Non-smoker Smoker	<0.0001
Wisnivesky JP, *et al.*	2007[24]	Women Men	<0.0001
Tokujiro, *et al.*	2008[26]	Never smoker Smoker	0.0314
Ryo, *et al.*	2011[25]	Ever smoker Never smoker	0.001
Present study	2011	Non-smoker Smoker	<0.001

As for the histology, our study found a significant difference between ADC and non-ADC in OS. Median OS was 12.5 months in the ADC and 10.0 months in the non-ADC groups (P < 0.001). The result also reached statistical significance in Cox model (P = 0.004). One reason that patients with ADC seem to survive longer may be smoking-associated. It is widely acknowledged that cigarette smoking is more strongly associated with squamous cell carcinoma than with ADC,[33] as was also observed in our study. Another reason for better ADC survival may be genetic and biological features. It has been shown in some studies that epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) mutations are associated with better clinical outcomes, almost entirely confined to the ADC population.[34,35]
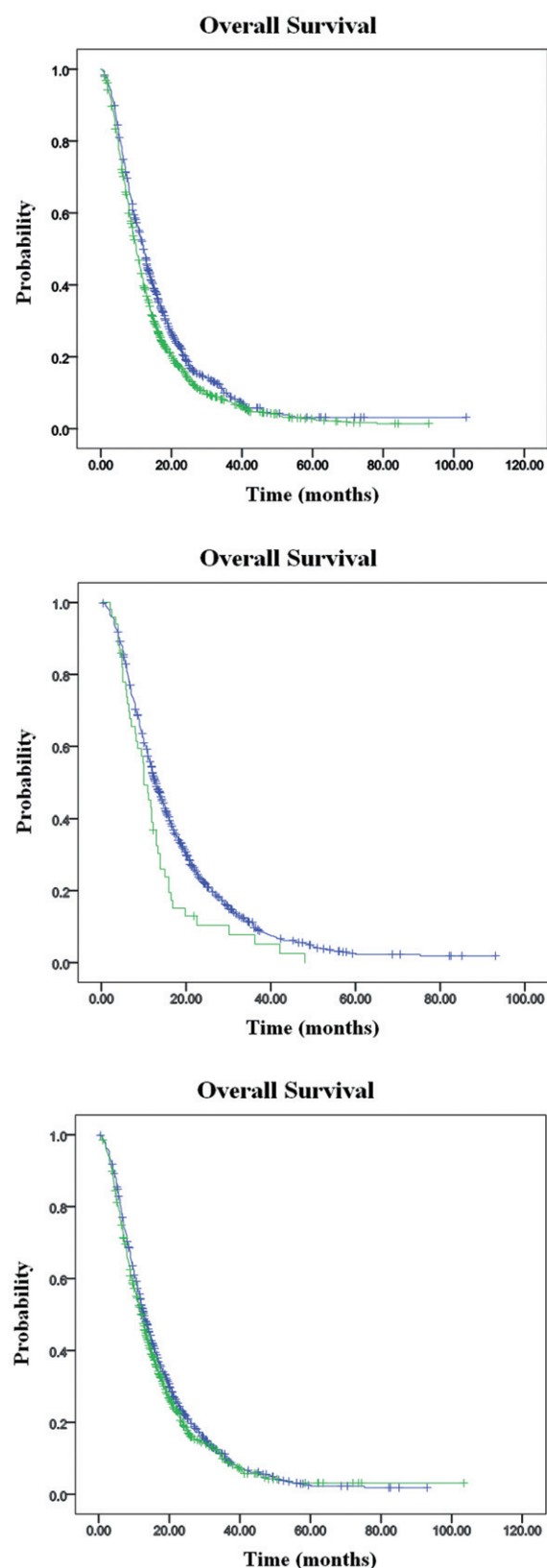
The limitation in our study is that we have 898 (20.8%) patients with NOS/mixed/others – a heterogeneous population. It is assumed that, if adequate tissue is obtained, a detailed analysis is more likely to be performed, thus obtaining a more distinct disparity between the ADC and non-ADC groups. Notably, the number of female non-smokers in our study is extremely small, which may lead to a bias in clinical outcomes.

Conclusion

In conclusion, we have demonstrated that non-smokers with NSCLC have an improvement in OS compared with smokers and that smoking status was a significant independent prognostic factor. Other independent prognostic factors, as identified in previous studies, were younger age (below 70-yrs) and ADC histology. We did not find gender to be an independent prognostic factor. Hopefully, our study will enhance the concept that NSCLC in non-smokers should be regarded and treated as a separate disease, with a seemingly better prognosis. Further research to clarify the molecular and biologic features of this distinct group is thus warranted.

Disclosure

No authors report any conflict of interest.

Overall Survival

A

Overall Survival

B

Overall Survival

C

Figure 2 (**a–c**) show the result of the comparison between non-smokers and smokers stratified by gender. (**a**): In male patients, non-smokers showed a better survival compared with smokers (median survival time [MST] 12.0 vs. 10.0 months, P < 0.001). Male: ⌐, non-smoker; ⌐, smoker; ╈, censor; ╈, censor. (**b**) Female non-smokers survive longer than smokers (MST 12.9 vs. 10.0 months, P = 0.012). Female: ⌐, non-smoker; ⌐, smoker; ╈, censor; ╈, censor. (**c**): In non-smokers, there is no difference between female and male patients (MST 12.9 vs. 12.0 months, P = 0.065). Non-smoker: ⌐, female; ⌐, male; ╈, censor; ╈, censor.
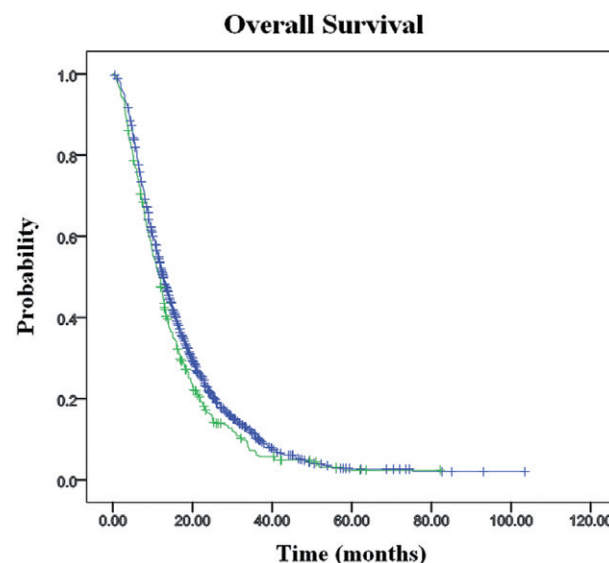
Overall Survival

Figure 3 Shows in non-smokers, patients under 70-years-old had a longer survival time than those above 70 (median survival time [MST] 12.8 vs. 11.7 months, P = 0.008). Non-smoker: ⌐, ≤70; ⌐, >70; ╈, censor; ╈, censor.

References

1 Sun X, Liu W, Wu S, Han H, Lin Y, Dai X. The morbidity and mortality trend and prediction of lung cancer in residents of Nangang District of Harbin in China during the past 10 years. *Chin J Lung Cancer* 2005; **8**: 514–17.

2 Jemal A, Bray F, Center MM *et al*. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69–90.

3 Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. *J Thorac Oncol* 2008; **3**: 819–31.

4 Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene* 2002; **21**: 7435–51.

5 Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin* 1995; **45**: 8–30.

6 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**: 347–51.

7 Yoshino I, Kawano D, Oba T, Yamazaki K, Kometani T, Maehara Y. Smoking status as a prognostic factor in patients with stage I pulmonary adenocarcinoma. *Ann Thorac Surg* 2006; **81**: 1189–93.

8 Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers – a different disease. *Nat Rev Cancer* 2007; **7**: 778–90.

9 Linden G, Dunn JE Jr, Hom PH, Mann M. Effect of smoking on the survival of patients with lung cancer. *Cancer* 1972; **30**: 325–8.

10 Holli K, Visakorpi T, Hakama M. Smoking and survival from lung cancer. *Acta Oncol* 1999; **38**: 989–92.

11 Toh C-K, Wong E-H, Lim W-T *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**: 1750–6.

12 Wheatley-Price P, Blackhall F, Lee SM *et al.* The influence of sex and histology on outcomes in non small cell lung cancer: a pooled analysis of five randomized trials. *Ann Oncol* 2010; **21**: 2023–8.

13 Hsu LH, Chu NM, Liu CC *et al.* Sex-associated differences in non small cell lung cancer in the new era: is gender an independent prognostic factor? *Lung Cancer* 2009; **66**: 262–7.

14 Itaya T, Yamanoto N, Ando M *et al.* Influence of histology type, smoking history and chemotherapy on survival after first-line therapy in patients with advanced non-small cell lung cancer. *Cancer Sci* 2007; **98**: 226–30.

15 Sandler A, Yi J, Dahlberg S, Kolb MM, Wang L, Hambleton J, Schiller J *et al.* Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of Bevacizumab with Paclitaxel/Carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol* 2010; **5**: 1416–23.

16 Mandrekar SJ, Schild SE, Hillman SL *et al.* A pooled analysis of 11 NCCTG advanced stage non small cell lung cancer (NSCLC) trials reveal the importance of baseline blood counts on clinical outcomes (Abstract 7193). *J Clin Oncol* 2005; **23**: 668.

17 Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC eds. *World Health Organization Classification of Tumors: Pathology and Genetics: Tumors of the Lung, Pleura, Thymus and Heart*. IARC Press, Lyon 2004.

18 Greene FL eds, Balch CM eds, Page DL eds *et al.* *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual, Sixth Edition*. American Joint Committee on Cancer, American Cancer Society, Chicago, NY 2002.

19 Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F. Chemotherapy vs supportive care in advanced non-small-cell lung cancer: results of a meta-analysis of the literature. *Chest* 1994; **106**: 861–5.

20 Feld R, Borges M, Giner V, Ginsberg R, Harper P, Klastersky J, Lacquet L, *et al.* Prognostic factors in non-small cell lung cancer. *Lung Cancer* 1994; **11**: 19–23.

21 Ou S-HI, Ziogas A, Jason A. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer and is independent of smoking status. *J Thorac Oncol* 2009; **9**: 1083–93.

22 Bryant A, Cerfolio RJ. Differences in epidemiology, histology, and survival between cigarette smokers and never-smokers who develop non-small cell lung cancer. *Chest* 2007; **132**: 185–92.

23 Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer – a decade of progress. *Chest* 2002; **122**: 1037–51.

24 Wisnivesky JP, Halm EA. Sex differences in lung cancer survival: do tumors behave differently in elderly women? *J Clin Oncol* 2007; **25**: 1705–12.

25 Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. The prognostic impact of cigarette smoking on patients with non small cell lung cancer. *J Thorac Oncol* 2011; **6**: 735–42.

26 Yano T, Miura N, Takenaka T *et al.* Never-smoking nonsmall cell lung cancer as a separate entity: clinicopathologic features and survival. *Cancer* 2008; **113**: 1012–18.

27 Toh C-K, Wong E-H, Lim W-T *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**: 1750–6.

28 Tsao AS, Liu D, Lee JJ, Spitz M, Hong WK. Smoking affects treatment outcome in patients with advanced non-small cell lung cancer. *Cancer* 2006; **106**: 2428–36.

29 Nakamura H, Ando K, Shinmyo T, Morita K, Mochizuki A, Kurimoto N, Tatsunami S. Female gender is an independent prognostic factor in non-small-cell lung cancer: a meta-analysis. *Ann Thorac Cardiovasc Surg* 2011; **17**: 469–80.

30 Liu NS, Spitz MR, Kemp BL *et al.* Adenocarcinoma of the lung in young patients: the MD Anderson experience. *Cancer* 2000; **88**: 1837–41.

31 Asmis TR, Ding K, Seymour L *et al.* Age and comorbidity as independent prognostic factors in the treatment of non-small cell lung cancer: a review of national cancer institute of Canada clinical trials group trials. *J Clin Oncol* 2008; **26**: 54–9.

32 de Rijke JM, Schouten LJ, ten Velde GP *et al.* Influence of age, comorbidity and performance status on the choice of treatment for patients with non-small cell lung cancer; results of a population-based study. *Lung Cancer* 2004; **46**: 233–45.

33 Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer* 2001; **31**: 139–48.

34 Shepherd FA, Rodrigues Pereira J, Ciuleanu T *et al.* Erlotinib in previously treated non-small cell lung cancer. *N Engl J Med* 2005; **353**: 123–32.

35 Kwak E, Bang Y-J, Camidge DR *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 1693–703.