RESEARCH ARTICLE

Risk Factors for Lung Cancer Mortality in a Referral Center

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Abstract

    <u>Background</u>: Lung cancer is one of the most common causes of death that is rising in many countries including Iran. This study aimed to determine the impact of factors on survival of lung cancer patients at a referral center of lung diseases in Tehran, Iran. <u>Materials and Methods</u>: A retrospective study was conducted on adult lung cancer cases admitted to a referral center for lung diseases from 2011 to 2015. Multivariate analysis was performed to determine the risk factors for all-cause mortality. <u>Results</u>: Of a total 933 patients with lung cancer, 53.4% died, 49.3% of them at the hospital. Overall median follow-up time was 7 months. The most common histological type of cancer was adenocarcinoma with a 13 month median survival time. Age ≥55 and smoking remained significant for all-cause mortality on Cox analysis, whereas gender was not. <u>Conclusions</u>: The survival of lung cancer patients is poor and the patients with history of smoking and age≥55 are at increased risk of death. Having a large hospital-based registry provides a good measurement of prognostic statistics for lung cancer. Further investigations are necessary to establish reasons for mortality.

Keywords: Lung cancer - mortality - survival - metastasis - Iran

Introduction

    Non-communicable diseases have increased astonishingly in most of countries (Parkin et al., 2005). The number of new cases of cancer registry is increasing worldwide and it has reached to 81% in Iran in 2006 according to the reports on Cancer Incidence in Five Continents database which is published by International Agency for Research on Cancer (IARC) (Parkin et al., 2005; Mousavi et al., 2009).

    Lung cancer is a major health dilemma in recent decades and causes of 1.6 million deaths from all cancers (Stewart, 2014). The most common causes of death in Iran are cardiovascular diseases, injuries, and cancers, respectively. In Iran, lung cancer is the second common cancer after stomach cancer among male patients based on population-based registry (Zendehde, 2011) . However, lung cancer among women is the third most common cancer in the world, in Iran is very low. Survival of lung cancer patients is still poor due to late diagnosis and losing the opportunity for complete therapy. The survival of lung cancer is estimated 10 -15% for all stages. Tobacco using, air pollution, exposure to carcinogens, genetic factors and other factors can cause lung cancer (Bilello et al., 2002; Lam et al., 2004; Lewtas, 2007).

    Although the reports of all cancers of many different sites (provinces and research centers) are provided in our

country, they are intermittent. The evaluation of outcome of lung cancer requires having a comprehensive and plenary program with a complete cancer registry system. Having a hospital-based cancer registry and following up the patients are necessary for changing and improving the survival of patients. The aim of this study was to determine the survival of lung cancer at a referral center of lung diseases and evaluate the characteristics of these patients in our hospital-based registry.

Materials and Methods

    A retrospective cohort study of lung cancer patients diagnosed was conducted at National Research Institute for Tuberculosis and Lung Diseases (NRITLD), from Jan 2011 to Dec 2015. This institute is the referral center for all kind of pulmonary diseases from all provinces of our country (including Tehran) and registers all new lung cancer cases in Tehran from 2010. The registry staffs visit the patients and provide the questionnaire according to IARC. The study protocol was approved by the NRITLD Scientific and Ethics Committee. All patients provided oral and written informed consent.

    Data on demographic, clinical history of patients, and paraclinical findings were recorded. The information was included the date of diagnosis, the location of tumor, morphology and histology of tumor, organ invasion,

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treatment modality, survival time and cause of death. Other kinds of tumors, recurrent and the cancers with lung metastasis were excluded from this study. The histological classification of lung tumors was described according to the World Health Organization guideline (Travis et al., 2015) and the staging performed based on the 7th edition of the TNM staging system published in 2009 (Sobin, 2010). The initial treatment was done at the hospital. All patients were followed up actively or passively to establish the vital status. Death certification was obtained from the hospital and the National Death Registry of Iran if the cause of death was mentioned as "Cancer" or "Tumor".

A total of 1086 cases, 938 patients with primary lung cancers were entered into the study and the rest of them were excluded of the study due to other type of cancer like mesothelioma (90 cases), thymoma (26 cases), and metastatic lung cancer with GI, Ovarian, and etc (32 cases). Also, five patients were excluded because of incomplete data of their tumor histology. Patients were divided into three groups based on their histological findings: *i*). Small cell lung cancer (SCLC); *ii*). Non-small cell lung cancer (NSCLC); *iii*). Other primary lung cancer (carcinoid, pleomorphic carcinoma, lung sarcoma).

Standard demographic and clinical information from patients' medical records were abstracted. Computerized tomography scan (CT scan) of brain and abdomen or magnetic resonance imaging (MRI) of brain, is done for all patients before initiation of chemotherapy and during their follow-up time if it is necessary. During of the study, the patients were followed every 6 month for present situation by telephone number. In addition, the oncologists visited the patients who chose this hospital for continuing their treatment and following up period. The time of last available information or the date of death was considered as time of follow up by month.

Categorical variables were compared using chi-square or Fisher's exact test and non-normally distributed continuous variables using the Mann Whitney U test. Survival analysis was used to compare survival time (month) in three groups based on histological type. A Kaplan-Meier survival analysis was performed between gender, age ≥55, the histological type of lung cancer and metastasis with all-cause mortality. Survival curves were compared using log-rank test with follow-up time. A Cox proportional hazards modeling was done to determine independent predictors of all-cause mortality for multivariate analyses. We included age≥55 yrs, gender, smoking, nationality, overall metastasis, and other factors if they were associated with mortality in bivariate analysis at p<0.2. All reported p values are two-sided. All data were analyzed using SPSS 16 [SPSS Inc, Chicago, IL, USA].

Results

Of 933 confirmed primary lung cancer during the study, the most common histological type was adenocarcinoma in 453 patients (48.6%) followed by squamous cell carcinoma (21.3%), small cell carcinoma (17%), large cell carcinoma (5.5%), non-small cell carcinoma (5%), and other type of cancers (2.6%) (Table 1). There were 498 deaths that 49.3% of them were at the hospital. Frequency of all type of lung cancer and the number of deaths in each year are shown in Figure 1. Overall median following time was 7 months (inter-quartile range [IQR] 3-13). The survival curves of all enrolled patients according to histological diagnosis is illustrated in Figure 2 (Log rank, p<0.001).

Of 253 female patients, 30 (5.5%) cases were smoker. Age ≥ 55, male gender and smoking were the characteristics associated with mortality in bivariate analysis (Table 2). Trend of death divided by gender is shown that the number of death and the number of lung cancer in both genders are rising (Figure 3). After adjusting for gender (Figure 4) and nationality in a Cox analysis;
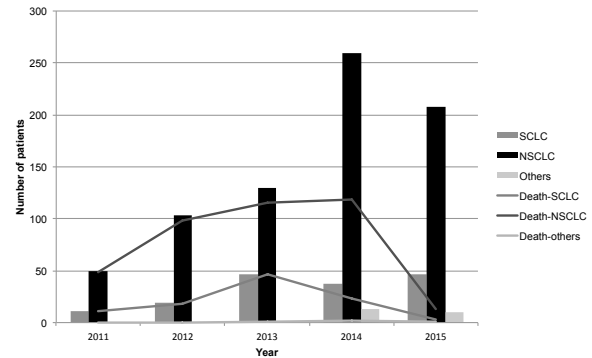

Figure 1. Frequency of Lung Cancer and Mortality According to Histological Type
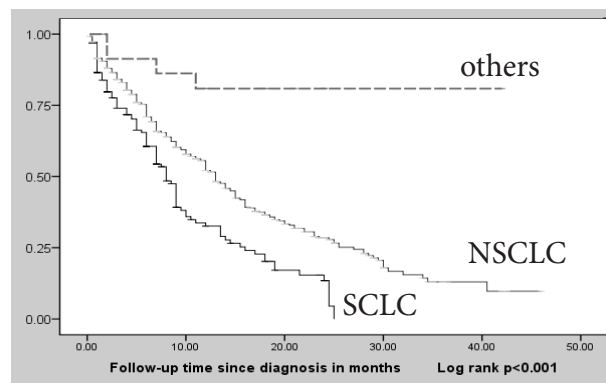

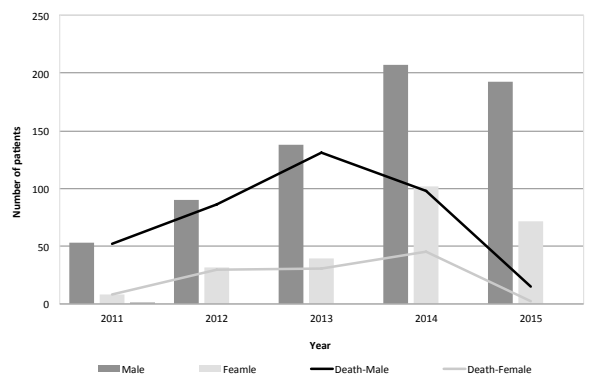**Figure 2. Survival of Lung Cancer Patients With Histological Diagnosis**

Figure 3. Trend of Lung Cancer Deaths According to Gender

Table 1. Histology of Lung Cancer and the Survival Time

Histology	Overall (n=933)	Median survival time (month;95%CI)†	Mortality		p-value*
			Yes (n=498)	No (n=435)	
SCLC	159 (17%)	8 (7- 9)	101 (20.3%)	58 (13.3%)	<0.001
NSCLC	750 (80.4%)	13 (12- 14)	393 (78.9%)	357 (82.1%)	
Others¥	24 (2.6%)	15 (7- 18)	4 (0.8%)	20 (4.6%)	

† The overall median survival time (month): 12 (11-13); * Kaplan-Meier was used and log rank p was < 0.001; ¥ Carcinoid, pleomorphic carcinoma, lung sarcoma; Abbreviation: SCLC, small cell lung carcinoma; NSCLC, non-small cell lung carcinoma

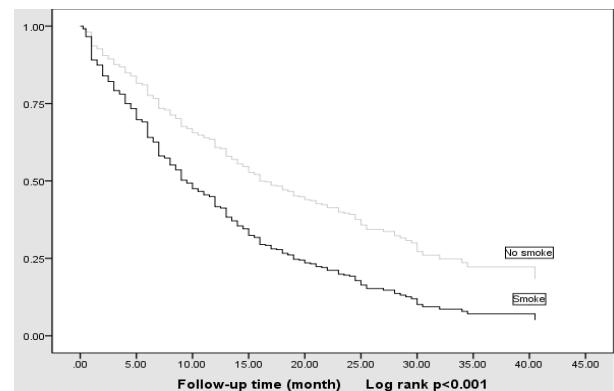**Table 2. Factors Associated with Mortality in Bivariate Analysis**

Characteristics	Overall (n=933)	Mortality		p-value*
		Yes (n=498)	No (n=435)	
Age (Mean± SD)	57.70± 12.54	59.70± 10.90	55.45± 13.90	<0.001
Age ≥ 55	599 (64.2%)	353 (70.9%)	246 (56.6%)	<0.001
Iranian nationality	904 (97%)	487 (98%)	417 (96%)	0.09
Male gender	680 (73%)	382 (76.7%)	298 (68.5%)	0.005
Urban residence	912 (97.7%)	483 (97%)	429 (98.6%)	0.09
History of smoking	550 (59%)	327 (65.7%)	223 (51.3%)	<0.001
History of opium use	282 (30%)	165 (33.5%)	117 (29.7%)	0.23
Passive smoker†	61 (16%)	32 (18.7%)	29 (13.7%)	0.18
Symptom duration (months)¥	8.7± 24.7	5.42± 9.80	10.54± 29.98	<0.001
NCC < 5 times	358 (46.7%)	228 (50.6%)	130 (41.1%)	0.01

* Student's t-test and x2 test or Fisher exact is used when appropriate; ¥ Mann-Whitney test was used; Abbreviation: OR, Odd's ratio; CI, Confidence interval; NCC, Number of chemotherapy course for 767 patients.
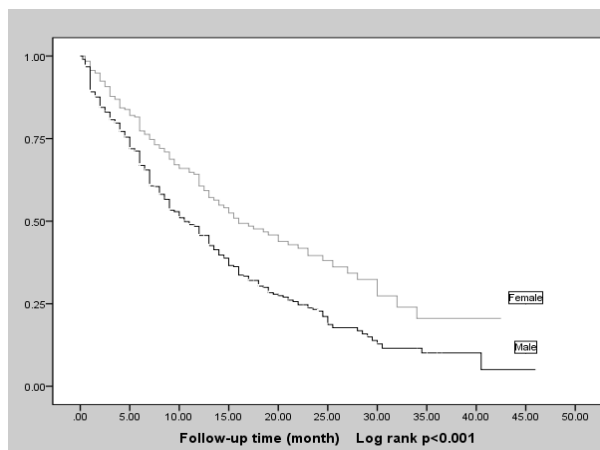
Figure 4. Survival of Lung Cancer Patients According to Gender
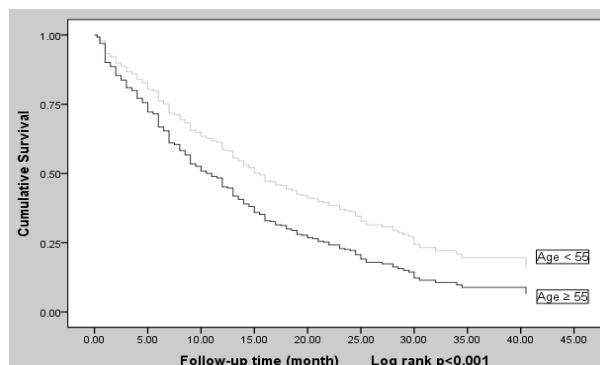
Figure 5. Survival of Lung Cancer Patients by Age ≥ 55

Figure 6. Survival of Lung Cancer Patients According to history of smoking

smoking (HR: 1.65, 95% CI: 1.36-2; p<0.001) and age ≥ 55 (HR: 1.49, 95% CI: 1.22- 1.81; p<0.001) remained independently associated with all-cause mortality (Figure 5 and 6).

The median course of chemotherapy was 5 times (IQR 2-8). Chemotherapy was done for 767 patients and surgery as a curative procedure was performed for 109 patients. Fifty five patients received just supportive and palliative care. Radiation therapy was used after chemotherapy for 217 patients.

Discussion

The quantity trend of lung cancer at our referral center was high during recent years. In addition, we had high mortality rate that it can be due to diagnosis of cancers in the advanced stage and high fatality rate of lung cancer. Duration of symptoms was significantly different between patients with and without death, so the higher mortality in these patients with short duration of symptoms is unlikely to be related to delayed diagnosis and it could be related to the advanced stage. Alternatively, we cannot exclude that the excess mortality was unrelated to cancer as autopsies are not routinely performed in our center and some patients did not die at hospital. However it should be considerate

that this study was hospital-based cancer registry and our center is a referral center for lung diseases. Also, the other types of cancer were eliminated in this study.

The risk factors of all-cause mortality investigated in several studies and it has varied according to hospital or population-based registry. In our study, there was significant difference between survival and gender in a bivariate (p=0.005) and in a Kaplan-Meier analysis (Log rank p<0.001), although after adjusting, it did not remain independently associated with mortality. Results of previous studies evaluating mortality are varied, with some reporting more association of mortality and male gender (Puri et al., 2010; Kefeli et al., 2011) and others showed no differences (Zahir and Mirtalebi, 2012).

SCLC and NSCLC (adenocarcinoma) are the most common histological type of lung cancer worldwide (Fu et al., 2005; Youlden et al., 2008). The type of lung cancer has changed over time from adenocarcinoma to squamous cell carcinoma (SCC). Some studies showed a better prognosis for SCC (Alexiou et al., 2002; Chansky et al., 2009) however the others found no significant difference in survival between SCC and others type of lung cancer (Janssen-Heijnen and Coebergh, 2001; Jemal et al., 2004; Puri et al., 2010). Adenocarcinoma was the most common histological type of lung cancer (48.6%) with a median survival time 13 month (95% CI: 11.8-14.2) in our study that it is similar to the study in Japan (Asamura et al., 2008) and recent studies in Taiwan (Wang et al., 2013) and Denmark (Wille et al., 2016a) . However, the other studies in our country showed that SCC was the highest prevalence of lung cancer (Najafi, 2010; Zahir and Mirtalebi, 2012; Hajmanoochehri et al., 2014).

Smoking is known as a major cause of increasing lung cancer and mortality. Recent studies documented that mortality is increased in patients with rising age, smoking history and history of lung diseases (Bach et al., 2003; Tammemagi et al., 2013; Luqman et al., 2014; Wille et al., 2016a; Wille et al., 2016b). These are similar to the finding of our current study where we have found association between mortality and smoking and older age (≥55).

Major strengths of our study are the evaluation of outcome of all lung cancer with tissue diagnosis in five years. In addition, large number of these patients provided to detect almost all factors related to the survival even if it was small. Despite the clinical implication of this report, the study has some limitations. It is undertaken in a referral center and it was performed on hospital-based cancer registry, so at least in part; our findings may not be representative of all lung cancer patients in our country. Nonetheless, it is likely that lung cancer patients treated in other centers with less or more expertise would have worse or better treatment outcome. Second, we did not consider the exact cause of death such as chronic diseases (heart failure, renal failure and others), injuries, syncope and others. Finally, we did not deem co-disease, food consumption, air pollution, and pollutant agents as a risk factor of death in the data analysis.

In summary, this study shows that age≥ 55 and smoking history are independently associated with death among patients. In addition, the survival of lung cancer

remains poor. Further studies are needed to clarify the reasons for excess mortality.

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