RESEARCH ARTICLE

Season of Diagnosis and Survival of Advanced Lung Cancer Cases - Any Correlation?

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Abstract

Introduction: The influence of season at diagnosis on cancer survival has been an intriguing issue for many years. Most studies have shown a possible correlation in between the seasonality and some cancer type survival. With short expected survival, lung cancer is an arena that still is in need of new prognostic factors and models. We aimed to investigate the effect of season of diagnosis on 3 months, 1 and 2 years survival rates and overall survival of non small cell lung cancer patients. Materials and Methods: The files of non small cell lung cancer patients that were stages IIIB and IV at diagnosis were reviewed retrospectively. According to diagnosis date, the patients were grouped into 4 season groups, autumn, winter, spring and summer. Results: A total of 279 advanced non small cell lung cancer patients' files were reviewed. Median overall survival was 15 months in the entire population. Overall 3 months, 1 and 2 years survival rates were 91.0%, 58.2% and 31.2% respectively. The season of diagnosis was significantly correlated with 3 months survival rates, being diagnosed in spring being associated with better survival . Also the season was significantly correlated with T stage of the disease. For 1 and 2 years survival rates and overall survival, the season of diagnosis was not significantly correlated. There was no correlation detected between season and overall survivals according to histological subtypes of non small cell lung cancer. Conclusion: As a new finding in advanced non small cell lung cancer patients, it can be concluded that being diagnosed in spring can be a favorable prognostic factor for short term survival.

Keywords: Lung cancer - non small cell - season - survival

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Introduction

Non small cell lung cancer (NSCLC) accounts for about 85% of overall lung cancer cases. Despite the progress in screening, diagnosis and treatment modalities; lung cancer is still the leading cause of death worldwide (Siegel et al., 2012). The majority of NSCLC patients present with advanced stage, only about 15-20% being early stage at diagnosis. At the moment, the best defined good prognostic factors for advanced NSCLC are, early stage disease at diagnosis, good performance status, having no significant weight loss and female gender (Finkelstein et al., 1986; Brundage et al., 2002). Since prognosis of patients with advanced disease is ominous overall and it is a group of heterogenous clinical entities; recent studies began to focus on identification of new prognostic factors (Efficace et al., 2006; Sequist et al., 2007). It is thought that, an accurate predictive model of survival can be useful for both providing answers to the patients' questions and deciding on correct treatment choices. At present most studies have focused on genetic predictive and/or prognostic factors as EGFR, EML-ALK4 and K-ras mutations, ERCC-1 and RRM-1 levels, that are mostly not applicable in most centers and are mostly expensive (Eberhard et al., 2005; Moscaux et al., 2005; Simon et al., 2005; Hwang et al., 2008; Reynolds et al., 2009; Shaw et al., 2009; Tsao et al., 2011).

The influence of season in which the cancers were diagnosed, on the outcomes of patients has been studied in several large epidemiologic studies (Lim et al., 2006; Porojnicu et al., 2008; Roychoudhuri et al., 2009; La Par et al., 2011). In most of these studies it has been shown that winter months are associated with poorer prognosis that may be explained through the variations in the cutaneous production of vitamin D3. In a few of those studies, lung cancer patients were included but there has not been a histopathological distinction made as small or non small cell lung cancer. We aimed to investigate the effect of the season of cancer diagnosis on both the short term as 3 months and longer as 1 and 2 years survival of the patients

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and also we decided to evaluate if it can be an independent prognostic factor in these group of patients with such a dismal prognosis.

Materials and Methods

The files of histologically proven non small cell lung cancer patients that were stages IIIB and IV at diagnosis were reviewed retrospectively. The age and gender of the patients, T and N stages and the final stage at diagnosis, the diagnosis date, histological subtypes and overall survival were recorded. According to diagnosis date, the patients were grouped into 4 seasons of diagnosis groups as autumn, winter, spring and summer.

Analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 18.0 statistical software. For patient and tumor characteristics, descriptive statistical methods were used. Chi-Square analyses were used to compare differences between categorical variables. Kaplan-Meier curves were drawn to obtain survival probabilities and log rank test was used to compare these curves between groups. Values are expressed as n (%), mean±SD or median (95%CI).

Results

A total of 279 non small cell lung cancer patients' files that were stages IIIB and IV at diagnosis were reviewed retrospectively. Thirty- four patients (12.2%) were female and 245 (87.8%) were male. Median age was 60 years (30-88 years). Histologically, adenocarcinomas represented 28.7% (n:80), squamous cell carcinoma 47.7% (n:133), non small cell (NOS) type 21.1% (n:59) of the cases. The rest 7 cases (2.5%) were large cell and bronchoalvelolar subtype. In 159 (57.0%) of the patients the stage at diagnosis was IIIB and in 120 (43.0%) of them it was stage IV. T stages were detected as T1 in 11 (3.9%), T2 in 58 (20.8%), T3 in 89 (31.9%) and T4 in 121 (43.4%) of the cases. N levels were N0 in 54 (19.4%), N1 in 21 (7.5%), N2 in 169 (60.6%) and N3 in 35 (12.5%) of the cases.

Table 1. The Season of Diagnosis in T, N and Overall Stages

		Spring	Summer	Autumn	Winter	p
Stage	IIIB (%)	32.1	23.9	18.2	25.8	
	IV (%)	22.5	28.3	19.2	30	0.357
T-stage	T1 (%)	9.1	18.2	54.5	18.2	
	T2 (%)	24.1	32.8	13.8	29.3	0.023
	T3 (%)	25.8	21.3	15.7	37.1	
	T4 (%)	33.1	26.4	19.8	20.7	
N-stage	N0 (%)	35.2	20.4	16.7	27.8	
	N1 (%)	14.3	38.1	19	28.6	0.406
	N2 (%)	26.6	26	17.2	30.2	
	N3 (%)	31.4	25.7	28.6	14.3	

Table 2. The Survival Rates According to Season of Diagnosis

Survival rates	Spring	Summer	Autumn	Winter	p
3 months (%)	30	24.2	20	25.8	0.046
1 year (%)	30.3	25.8	18.2	25.8	0.842
2 years (%)	32.7	25	19.2	23.1	0.798

The frequencies of the season of diagnosis according to T, N and overall stages are shown in Table 1.

The difference between the season of diagnosis according to stages IIIB and IV wasn't found to be significant (p 0.357). According to T stages, it was found that more than half of the T1 disease patients were diagnosed in autumn. T3 and T4 disease were more commonly diagnosed in winter and spring, respectively. The difference between T stages of the patients and the season of diagnosis was found to be significantly correlated (p 0.023). But for the difference between N stage and the season, no significance was detected (p 0.406).

Median overall survival was 15 (12.33- 17.67) months in the entire population. Overall 3 months, 1 and 2 years survival rates were 91.0%, 58.2% and 31.2% respectively. In stage IIIB median survival was 18 (15.45-20.55) months and it was 10 (7.68-12.32) months. The difference between median survivals in stages IIIB and in stage IV it was 10 statistically significant (p<0.001).

The season of diagnosis was spring in 78 (28.0%), summer in 72 (25.8%), autumn in 52 (18.6%) and winter in 77 (27.6%) of the patients. Three months, 1 and 2 year survival rates according to the season of diagnosis are shown in Table 2. There was a significant difference in between 3 months survival rates according to the season of diagnosis (p 0.046). For 1 and 2 years survival rates a significant difference was not present.

In stage IIIB patients, the median overall survivals according to the season of diagnosis (spring, summer, autumn and winter) were 17.0 (10.41-23.59), 21.0 (15.13-26.87), 19.0 (11.95-26.05) and 17.0 (14.68-19.31) months respectively. The survivals of the patients according to the seasons are shown in Figure 1A. There was not a significant difference between survivals according to the season of diagnosis of the patients with stage IIIB disease (p 0.686).

In stage IV patients, the median overall survivals

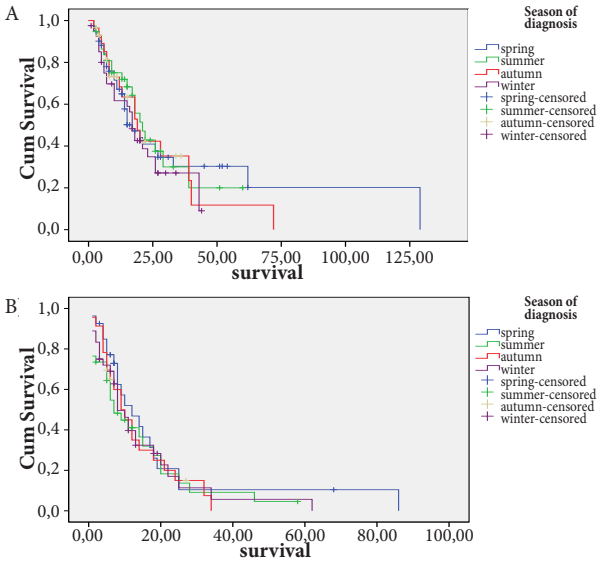

Figure 1. The Survival Curves in A) Stage IIIB and B) Stage IV Patients According to Seasons of Diagnosis

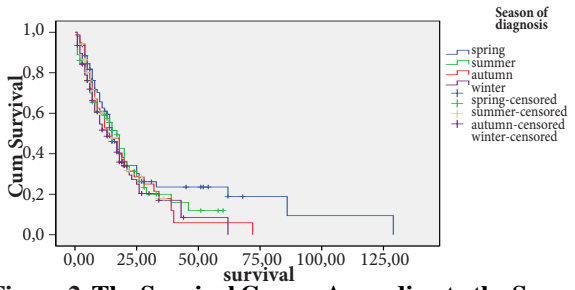

Figure 2. The Survival Curves According to the Season at Diagnosis

according to the season of diagnosis (spring, summer, autumn and winter) were 12.0 (5.15-18.49), 7.0 (3.47-10.53), 9.0 (4.58-13.24) and 8.0 (5.03-10.97) months respectively (Figure 1B). There was not a significant difference between survivals according to the season of diagnosis of the patients with stage IV disease (p 0.518).

According to the patients' season of diagnosis, median overall survival values were 15.0 (12.9-17.81) months for the cases that were diagnosed in spring, 17.0 (13.09-20.91) for summer, 14.0 (8.22-19.78) for autumn and 13.0 (7.68-18.32) months for winter (Figure 2). Median survivals were poorer for the patients who were diagnosed in winter but the difference between survivals according to the seasens was not statistically significant (p 0.436). Median overall survivals were not different in between the histological subtypes (adeno, squamous, NOS and other groups) according to the season of diagnosis (p 0.568). Three months, 1 and 2 years survival rates in each histological subtype were not significantly correlated with season of diagnosis (p>0.05).

Discussion

In the present study, we have found that the season of diagnosis in advanced NSCLC patients is correlated with 3 months survival rates. For the cases that were diagnosed in spring, short term survival rates were higher than other seasons. But for 1 and 2 year survivals, the season of diagnosis was not found to be a significant prognostic factor in advanced NSCLC patients. The possible explanation for the relation between season of diagnosis and short term mortality in this study may be; in that early period after diagnosis, mostly deaths are attributable to treatment related complications that may be in close relation with seasonal variations. Autumn and winter periods are associated with increased incidence of pulmonary infections and other cardiopulmonary complications, especially for those with comorbidities such as chronic obstructive pulmonary disease or heart diseases (Eccles, 2002). For lung cancer patients the risk of respiratory tract infections increases additionally, because of both tumor with its regional effects and high prevalence of smoking related comorbidities causing higher rates of bronchial colonization that together form a suitable environment for the development of infection. The risk increases for patients on chemotherapy and/or radiotherapy because of the probable treatment related decreases in bone marrow adequacy and increased risk of neutropenia and neutropenic fever that amplifies seasonality. So it can be thought that, being diagnosed in spring can be a favorable prognostic factor for 3 months survival rates. To our knowledge, this is the first study that has evaluated the effect of season of diagnosis on survival in only advanced NSCLC patient group.

Several studies investigated the effect of season of diagnosis on survival in some cancer types. The protective role of sunlight in cancer incidence was first suggested by Apperly, (1941) as an inverse relation between sun exposure and cancer incidences. Later, by the studies on colon cancer patients, it was proposed that the role of season may be related to a mechanism involving Vitamin D metabolism (Garland and Garland, 1980; Garland et al., 1989). Some in vitro and in vivo studies support the hypothesis that 1,25 dihydroxy-cholecalciferol regulates cell differentiation and proliferation and exerts antiproliferative effects and this underlie the observed seasonality in cancer survivals (Ordonez-Moran et al., 2005).

In the study by Rossahm et al. (2004), breast, colon and prostate cancer patients were evaluated and survivals of those diagnosed in winter were compared with other 3 seasons. They found that the relative risk of cancer death diagnosed in summer and autumn were lower compared to winter and there was a statistically significant dependence of survival on season of diagnosis.

Mutlu et al. (2013) have evaluated if season was an independent prognostic factor in breast cancer patients and they have suggested that it was not an independent prognostic factor for overall survival. However different from other studies, in that study, the patients diagnosed in winter were found to have significantly better DFS times (p 0.019).

Kaiser et al. (1996) studied the expression of vitamin D receptor in human lung cancer (both small and non small cell types) cell lines and demonstrated vitamin D receptor expression in both lung cancer types. They concluded that a subset of lung cancer patients may be susceptible to the differentiating effects of vitamin D analogues. Later Yokomura et al. (2003) found higher levels of 1 alpha hydroxylase activity in alveolar macrophages of lung cancer patients when compared with control group. In subgroup analysis, in advanced stage cases (IIIB and IV) the expression of 1 alpha hydroxylase gene was the highest, followed by early stage and then the control group. However, in our study, for 1 and 2 years survival rates, a significant correlation with seasonality was not detected for advanced NSCLC cases.

Lim et al. (2006) analyzed the effect of sunlight exposure and season of diagnosis and sunlight exposure on more than a total of a million colorectal, lung, breast and prostate cancer patients. They have found that, patients diagnosed in summer and autumn showed prolonged survivals than those diagnosed in winter, especially in lung and breast cancer patients. This seasonal variation was significant for survival for both sexes in lung cancer patients. Sunlight exposure was also found to be a predictor of cancer survival, but a weaker one than season of diagnosis. But in this study for lung cancer patients, non small and small cell types were not set apart and also the stages of the patients were not taken into account.

In a recent study, the effect of seasonal variation on postoperative outcomes for more than 180 000 lung cancer patients undergoing lung resections was evaluated. It was found that lung cancer resections in spring confer the lowest risk of mortality (La Par et al., 2011). In our study, the patients were all stage IIIB and IV patients.

Roychoudhuri et al. (2009) investigated the effect of season of cancer diagnosis on short term (1-month) and long term survivals (>5 years). For the first month, those diagnosed in summer were shown to have better survival rates that is most striking in breast cancer patients [HR:0,81 (0.75-0.86)] for the ones in summer in breast cancer patients). In lung cancer patients HR for 1 month survival was 0.86 (0.82-0.90) for the ones diagnosed in summer. For long term (>5 years) survivals, there was a shift in seasonality detected, as diagnosis in autumn being associated with reduced mortality in long term survivals especially for lung cancer patients (HR: 0.89 (0.80-0.99) for lung cancer). They have concluded that higher survivals in cancer patients diagnosed in summer and autumn, reported in most studies may be due to a short term effect and that this issue depends on a number of different factors that should be investigated separately in each country or health care system.

In our study we have also found that 3 months survival rates were correlated with season of diagnosis in advanced NSCLC patients, as spring diagnosis being the best for short term survival. We could not detect any correlation with seasonality and 1 and 2 years survival rates or overall survivals. So we thought that the role of season of diagnosis in advanced stage NSCLC prognosis is not a field that can be so strongly and solely linked to vitamin D. It may be related to many different clinical and biological parameters that need to be investigated. For different histological subtypes of NSCLC, overall survivals were not correlated with the season of diagnosis. It can be concluded that for advanced NSCLC patients, being diagnosed in spring, can be a favorable prognostic factor for only 3 months survival rates.

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