

## RESEARCH ARTICLE

# Survival of Patients with Lung Cancer, Yazd, Iran

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### Abstract

**Background:** Lung carcinoma is the leading cause of cancer mortality worldwide. Although the 5-year survival rate nearly tripled from 5-15% over the last 25 years, the estimated number of deaths still exceeds 1.3 million annually. The overall 5-year survival of lung cancer is only 10% in Europe and 15% in the United States. The aim of the current study was to determine the long-term survival and the effect of certain prognostic factors on survival of patients with lung cancer in Yazd city, Iran. **Methods:** In this cross-sectional descriptive study, we retrospectively reviewed hospital records and follow-up data of 148 patients with histological proven lung cancer using the cancer data registered between 1998 and 2005 in the pathology department of Shahid Sadoughi educational hospital, Yazd, Iran. Data were extracted from patient documents that included sex, age, clinical manifestations, histopathological report of the tumor and type of treatment given. **Results:** Overall survival time in all patients was 8.5 months after diagnosis and there was no significant difference in survival according to sex ( $p=0.958$ ). Histological analysis revealed that squamous cell carcinoma was the most common histologic type (35%). Kaplan-Meier statistical methods estimated the average survival time for SCC to be better (22.6 months) in comparison with the other types of histology (all of them below 10 months). There was a trend towards significance between type of histology and duration of survival ( $p=0.08$ ). **Conclusion:** It is reasonable to expect that early lung cancer detection, and appropriated treatment, may improve surgical morbidity and mortality. Low survival of lung cancer in our center patients show our shortages in screening programs for early diagnosis. Designing studies with larger sample size that take some other variables like staging of patients is now necessary.

**Keywords:** Carcinoma - lung - prognosis - survival - Iran

*Asian Pacific J Cancer Prev*, 13 (9), 4387-4391

### Introduction

Lung cancer is the leading lethal cancer during men and women and more than 80% of patients will die during first five years of diagnosis. High incidence and also poor prognosis (even with new developments in cancer treatment) causes lung cancer to be a major health problem during past decades. Lung cancer is cause of 32% and 20% of all deaths from cancer between men and women respectively (Fraser et al., 1994; Horn et al., 2012). The most common age for incidence of lung cancer is 55-65 years (Horn et al., 2012).

About 90% of cases are diagnosed by clinical presentation while diagnosis in other 10% is accidental. In most of cases, patient will undergo surgeries for resection based on paraclinical diagnosis results, but because of non sensitive and high cost paraclinical diagnostic modalities, during surgery extensive invasions and metastasis was not proved by previous diagnostic tests will be detected. In these stages patients are poor prognosis. Based on pathology, lung cancer has several cellular types, that have different responses to treatment, and then the first step in diagnosis is based on histological study. According to World Health Organization (WHO) primary malignancies

of lung are divided into eight main groups (Fraser et al., 1994).

About 88% of lung tumors will be included in four cellular types, Squamous Cell Carcinoma, Adenocarcinoma, Large Cell Carcinoma and Small Cell Carcinoma. Based on information from some countries, adenocarcinoma is the most prevalent type during men and women and also all races, and replaced the Squamous Cell Carcinoma, of course prevalence of Adenocarcinoma and Small Cell Carcinoma (especially during women) is increasing (Choi et al., 1990; Cristiano, 1997; Strauss, 1997). But based on Iranian studies the highest prevalence is still for Squamous Cell Carcinoma (Ehteshamifar et al., 2001; Najafi et al., 2010).

Squamous Cell Carcinoma and small cell carcinoma presents with central masses and have endobronchial growth, while Adenocarcinoma and Large Cell Carcinoma have peripheral masses or nodules with pleural involvement (Horn et al., 2012).

#### *Risk factors of lung cancer*

Smoking is the most important cause of lung cancer and is related to incidence of all types, but is most related to Squamous Cell Carcinoma (especially in women) and

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small cell carcinoma (Choi et al., 1990; Fraser et al., 1994; Cristiano, 1997; Strauss, 1997; Horn et al., 2012). Smokers are 10-20 times more at risk for lung cancer contrasting with general population but from each 10 heavy smokers only one will develop lung cancer. The numbers of cigarettes and duration of smoking (Pack years), cigarette type and the time of smoking start are some of the most important factors in lung cancer development (Armandas-Gil et al., 1999; Boffetta et al., 1999; Leonard and Sachs, 1999; Speizer et al., 1999; Rapiti et al., 1999; ). Occupational factors like pollution (arsenic, asbestos, nickel, radiation and vinyl chloride), nutritional factors (vitamins A, E and C) and some predisposing factors in patient are other important risk factors (Bepler, 1999; Droste et al., 1999; Greenberg, 1999; Jahn et al., 1999; Lee et al., 1999; Morinaga et al., 1999; Pellegrini et al., 1999; Pezzotto and Poletto, 1999; Prescott et al., 1999; Ronneberg et al., 1999; Wakai et al., 1999; Zhou et al., 1999). Although smoking is important in all types of lung cancer but its effect on squamous cell carcinoma in men and small cell carcinoma in women is more proven (Ernester et al., 1994). Recent studies suggested that lung diseases like emphysema, bronchitis and asthma can cause lung cancer (especially squamous cell carcinoma at old ages) (Mayne et al., 1999).

### *Etiology*

The leading factor in lung cancer development like any other malignancy is disturbance in regulation of cell division (mitosis). Origin of about 90% of lung cancers is increase in structural changed basal epithelium and lung squamous cells.

Squamous cell carcinoma (epidermoid carcinoma) accounts for about 30 or 40% of primary lung tumors. They grow most commonly in the central areas in or around major bronchi. They grow in a stratified or pseudoductal arrangement; the cells have an epithelial pearl formation with individual cell keratinization. These tumors deposit keratin, and as they grow develop a necrotic, keratinous mass which appears cheesy on dissection (WHO, 1981). Widespread Metastases occur relatively late. Some results can be achieved if slow growing and treated with radiotherapy.

Adenocarcinomas arise peripherally from mucous glands and the cells retain some of the tubular, acinar or papillary differentiation and mucus production (WHO, 1981). They commonly invade pleura and mediastinal lymph nodes and often metastasise to the brain and bones. They bear similarity to secondary tumours and must be distinguished by CT scans and other investigations to check for presence of a primary. Adenocarcinoma commonly arises around scar tissue and is also associated with asbestos exposure. One form of adenocarcinoma is often distinguished from others, bronchiolo-alveolar carcinoma; these characteristically have well differentiated 'bland' cells which grow along alveolar ducts. Adenocarcinomas are proportionally less common in non-smokers.

Large cell carcinoma metastasizes early and may simply be considered to be those cancers which do not fit into the categories above. Close study by electron microscopy indicates that these types can probably be

included with squamous or adenocarcinomas.

Small (Oat) cell carcinoma accounts for about 20-30% of all lung cancers, these cells secrete a large amount of polypeptide hormones, thought to be as a result of their development from cells of the APUD system. This produces extra-pulmonary manifestations such as SIADH and ectopic adrenocorticotrophin syndrome. This form of lung cancer is responsive to chemotherapy. Under the microscope they form sheets of darkly staining cells with prominent nuclei and little cytoplasm (WHO, 1981) their secretory activity can be seen as the presence of neurosecretory granules in the cytoplasm seen by electron microscopy. This form is very strongly linked to smoking as a causative factor.

Symptoms and signs that may suggest lung cancer like coughing, weight loss, dyspnea (shortness of breath), chest pain, hemoptysis (coughing up blood), bone pain, clubbing of the fingernails, fever, fatigue, Superior vena cava obstruction, dysphagia (difficulty swallowing) and wheezing (Horn, 2012). Depending on the type of tumor, so-called paraneoplastic phenomena may initially suspect physician to disease (Honnorat and Antoine, 2007). These phenomena In lung cancer may include Lambert-Eaton myasthenic syndrome (muscle weakness due to auto-antibodies), hypercalcemia, or syndrome of inappropriate antidiuretic hormone (SIADH). Tumors in the top (apex) of the lung, known as Pancoast tumors, may invade the local part of the sympathetic nervous system, leading to Horner's syndrome as well as damage to the brachial plexus (Horn et al., 2012).

Cytology and histopathology are the most prevalent ways to diagnose and follow the lung cancer. These methods have high diagnostic sensitivity and specificity but false negative has been reported (Linder, 2000). Also bronchoscopy is a standard way for diagnosis (Postmus, 2005). Other screening modalities are Chest x-ray, MRI and CT scan and also serum tumor markers (Misciasci, 2004; Schneider, 2006).

Estimations shows that there are about 1.3 million deaths of lung cancer annually worldwide (Berrino et al., 1999) and about 90% of diagnosed cases in Europe will die during 5 years of diagnosis (Kasper et al., 2007).

Because there was no study on survival of lung cancer in Yazd province, and even our country, Iran, In this study we tried to detect five years survival of lung cancer according to type of tumor, sex, age and treatment protocol to compare its Results with other studies in the country and also in the world to draw a more detailed landscape for screening, prevention and treatment of lung cancer patients.

### **Materials and Methods**

This descriptive analytic survival study was done on all registered patients with primary lung cancer in Shahid Sadoughi and Shahid Rahnemoon educational General Hospitals during 1998-2005 (totally 170 patients was admitted). Twelve patients which their documents were not complete were excluded from the study. Inclusion criteria's were positive cytology (from broncoscopy or pleural fluid aspiration). Histopathologic type of cancer

from patients who had definitive diagnosis was registered in the hospital documents were taken and registered in study forms based on WHO classification (eight patients had no definitive diagnosis). Also age, sex, smoking, main complaint of patient at the time of primary admission, time of diagnosis and treatment was done for patients were registered in the questionnaire form. Telephone number of patients for follow up was taken too. Researcher called to all patients and present situation of patients was asked, if patients was dead the time and cause of death was asked too. If researcher was unsuccessful in connection to patients, the patient was included in the study analysis as loss to follow up and the time of last available information was taken as time of follow up. These findings were recorded using a standardized data collection forms. Probability of survival was then analyzed with the Kaplan-Meier method. The significance of differences between subgroups was calculated using the log-rank test. The Cox model was used for multivariate analyses.

## Results

Totally 148 patients were included in the study, 109 men (73%) and 39 women (27%) (male/female=2.79). mean age of patient was 63±12.8, that was 63.8±11.8 in men and 60.7±15.2 in women (P=0.198) (Table 1).

About clinical presentation cough was the most prevalent complaint and fever had lowest prevalence. Based on Cox regression statistical model there were no relation between clinical presentation and survival and there was no specific clinical presentation that has considerable effect on survival. Survival was analyzed by Kaplan-Meier test (Table 2).

Cox-regression statistical model was used for studying the effect of different variables on survival. Only about 25% of patients had survival more than one year (26.6% of women and 26.6% of men) that was not significant (P=0.958; Log Rank). Mean survival duration for all patients in this study was about 8.5 months. The one, two and three year's survival of patients in this study is indicated in Figure 1.

About half of patients (48.3%) were more than 65 years old (Male/Female=3.17) and 8.7% of patients were younger than 45 years old (Male/Female=1.16). With increasing age the survival was decreased significantly (P<0.001; Log Rank).

Squamous cell carcinoma was the most prevalent tumor type (34.9%) and adenocarcinoma was the second (23.5%). Small cell and metastatic carcinoma were at next rank and account about one third of all tumors. Large cell

**Table 1: Age Distribution of Patients with Lung Cancer**

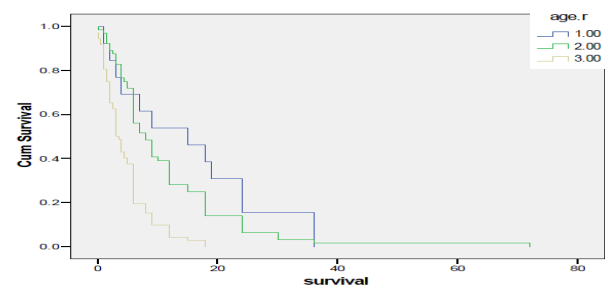
Age group	Male	Female	Total
25-34	1 (0.90%)	2 (5.10%)	3 (2%)
35-44	6 (5.60%)	4 (10.30%)	10 (6.80%)
45-54	18 (15.70%)	6 (15.40%)	23 (15.50%)
55-64	30 (27.80%)	10 (25.60%)	40 (27.70%)
65-74	31 (28.70%)	8 (20.50%)	39 (26.50%)
>75	23 (21.30%)	9 (23.10%)	32 (21.60%)
Total	109 (73%)	39 (27%)	148 (100%)

**Table 2: Clinical Presentations Related Survival and P-Values (Kaplan-meier test)**

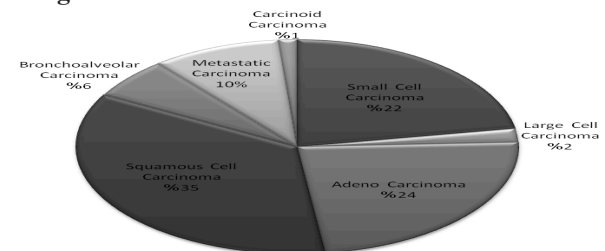
Clinical presentation (CP)	Absence or presence of CP	Mean survival duration	P-Value
Cough	Yes	8.7	0.752
	No	8.1	
Dyspnea	Yes	8.6	0.819
	No	8.1	
Wight loss	Yes	8.2	0.766
	No	8.9	
Hemoptysis	Yes	8.2	0.947
	No	8.5	
Fever and shivering	Yes	9.1	0.674
	No	8.4	

**Table 3. Effect of Treatment on Lung Cancer Survival**

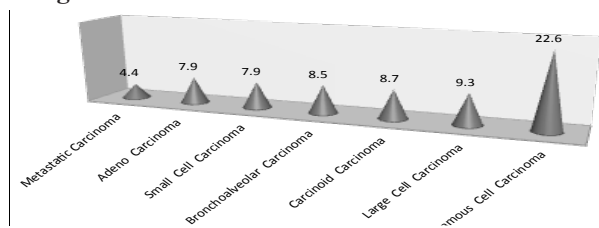
Treatment	Frequency	%	Mean Survival	Standard Error	Median survival	Standard Error
Only surgery	8	5.4	6.9	2.6	1.5	3.5
Only chemotherapy	40	27%	5.2	0.7	3	0.3
Only radiotherapy	0	0	-	-	-	-
Surgery and chemotherapy	31	20.90%	7.30%	0.7	6	0.5
Surgery and radiotherapy	0	0	-	-	-	-
Chemotherapy and radiotherapy	24	16.20%	6.3	1.3	4.5	0.6
Surgery, chemotherapy and radiotherapy	31	20.90%	19.4	2.3	18	2.3
No treatment	14	9.60%	1.3	0.4	1	0.3



**Figure 1. Survival of Lung Cancer Patients According to Age.**



**Figure 2. Frequency of Histopathology of Patients with Lung Cancer.**



**Figure 3. Survival of Patients with Lung Cancer According to Pathologic Type (Survivals are Indicated by Month).**

carcinoma, carcinoid tumor and bronchial gland tumor accounts about 10% of all tumors (Figure 2). There was no significant relation between pathology and survival ( $P=0.08$ ; Log Rank (Mantel-Cox)). Highest survival was for squamous cell carcinoma (22.6 months) and lowest was for metastatic cancers (4.4 months) (Figure 3).

About 60% of all patients were smokers but only one woman was between them and the others were men. There was no significant relation between smoking and survival ( $P=0.085$ ; Log Rank) (Table 8).

About 47% of patients were undergone surgery for resection and about 85%, got chemotherapy courses (despite the frequency of sessions) as mono therapy or as a part of combination therapy. Fourteen patients (10%) did not use any therapy while about 31 patients (20%) got all three available treatment modalities (surgery, chemotherapy and radio therapy), that mean survival duration was higher in this group contrasting with others ( $P=0.0001$ ; Log Rank). Also patients who were undergone surgery had higher survival significantly ( $12.6\pm 1.3$  Vs  $4.8\pm 0.6$ ,  $P=0.0001$ ; Log Rank).

## Discussion

Based on our study mean age of subjects was  $63\pm 12.8$  that was matched with results from other countries (Arrieta et al., 2012; Gilbert et al., 2012). The most prevalent clinical presentation was cough and the less prevalent fever.

In our study there was no significant difference between survival according to sex, while in most of previous studies sex is one of the effective factors on survival, for example Battafaro. et al (Battafarano et al., 2002) after study on 451 patients resulted that survival in women is higher than men, Puri V concluded similar results in his study too (Puri, 2012). Of course Kefeli et al. in turkey concluded that women only in adenocarcinome have higher survival than men (Kefeli, 2011).

We have detected significant relation between age and survival. Survival is lower in old ages. This result was confirmed in other studies too (Puri et al., 2012).

In our study and also in other studies in Iran like Ehteshamifar et al and Najafi et al studies (Ehteshamifar et al., 2001; Najafi et al., 2010) Squamous cell carcinoma is the most prevalent lung malignancy in Iran and adenocarcinoma and small cell carcinoma are next in rank. These results in comparing with results of other countries are different. During recent years most of studies accounts Adenocarcinoma as the most prevalent tumor. Charloux A and Haraguchi S had such results (Charloux et al., 1997; Haraguchi et al., 2012). Histopathologic diagnosis in this study and also in other studies in Iran was based on broncoscopy specimen. Squamous cell and small cell carcinoma have central masses with endobronchial growth while adenocarcinoma and large cell carcinoma have peripheral and pleural involvement and it is possible to miss the peripheral masses. On the other hand low numbers of pleural or open lung biopsy show the low prevalence or high mortality of these tumors before diagnosis. It is notable that the second grade in our

prevalence ranking is for adenocarcinoma that shows the need for a multicentre study with larger sample size to detect the most prevalent lung malignancy more precisely.

There were no significant relation between tumor cellular type and survival, but the higher survival was for squamous cell and the lower was for metastatic carcinomas. These results don't confirm other article like Read WL study in US which calculated higher survival for adenocarcinoma (Read et al., 2004).

Our study results and also other similar studies (Berghmans et al., 2005; Eberhardt et al., 2009; Marra et al., 2011) show that mean survival of patients who used combination of surgery, chemotherapy and radio therapy was higher than other treatments significantly. Chemotherapy with surgery and chemotherapy were at next ranks.

What needs more attention is our lower survival (8.5 months) comparing with other studies (Kawaguchi et al., 2010; Santoro et al., 2011). Considering with dramatic difference between survival in our study and lack of similar studies in Iran, designing studies with larger sample size that take some other variables like staging of patients is necessary. This big gap if show our insufficiency in screening or treatment, need more evaluation and consideration. Also we need registry centers in our referral centers to do better follow ups for our patients.

## Acknowledgements

Authors would like to appreciate Dr Masoud Rahimian Shahreza for his special guidelines in writing the dissertation. Also we must thank from Dr. Behnam Baghianimoghadam for his consultation in writing and publication of article. Conflict of interest and financial support, this study was under financial support of faculty of medicine, Shahid sadoughi University of medical sciences, Yazd, Iran as part of Mrs. Maryammosadate Mirtalebi dissertation to be graduated in General medicine. Other authors declare no conflict of interest.

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