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Clinicopathological Features of Patients with Non-small-cell Lung Cancer in West of Iran

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ABSTRACT

Background: Lung cancer is the most common cause of cancer death worldwide with an annual mortality rate of more than 1.3 million worldwide. We aimed to analyze the clinicopathological features of patients with non-small-cell lung cancer (NSCLC) in west of Iran.
Methods: 64 patients with NSCLC who referred to our clinic were analyzed. Sex, age, histopathology, location of the tumor, treatment, sites of metastasis and overall survival of the patients were studied. EGFR mutations were analyzed using th DxS kit with Multiplex allele specific real-time PCR×29 primers (ARMS Method), DxS Scorpion and ARMS assay.
Results: Mean age of the patients at diagnosis was 60 years. 51 (79.7%) patients were men. 34.3% were in their sixth to seventh decade of life (50-69 years). 40 (68.75%) patients had distant metastasis to bone and liver as the most common sites. Adenocarcinoma, squamous cell carcinoma and large cell carcinoma were observed in 68.8%, 23.3%, and 7.9% of the patients, respectively. 3-year survival rate was 25% and the mean overall survival (OS) was 16 months for all patients.
Conclusion: The mean age of Iranian patients with lung cancer in a western province of Iran was between 55-65 years in our study. Metastasis to bone was more common than other studies. Also, the OS in this study was higher than the other studies.

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Introduction

Lung cancer is one of the most common types of cancers in both genders with a dismal outcome.[1] It has been estimated to have a five-year overall survival rate of <15%,[2] with a rate of 2-22% for patients with stage IIIb-IV.[3] In Iran, it ranks as the second and third cancer-causing death in men and women, respectively.[4] Lung cancer accounted for 18.2% of all cancer deaths worldwide in 2008, with an age-standardized mortality rate of 19.4 per 100,000.[5] Lung cancer incidence decreased more rapidly among men than women and more rapidly among adults aged 35-44 years than other age groups.[6] Lung cancer is divided into two main histological types, where non-small cell lung cancer (NSCLC) comprises around 85% of the cases and small-cell lung cancer (SCLC), the remaining 15% of the cases.[7,8]

Maintenance therapy, whether in switch or continuation is beneficial in patients with advanced NSCLC who have received up to four cycles of a platinum-containing regimen. After detection of the role of the epidermal growth factor receptor (EGFR) mutations in lung cancer, despite much debate regarding the results of the different studies and reserved improvement in survival, pembrolizumab and erlotinib are approved and being used for maintenance therapy in many countries.[9] Based on the "oncogene addiction" theory, development of

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new compounds targeting tumor-driving pathways (e.g., EGFR signaling pathway) has been promising in the treatment of malignant tumors.[10,11] Identification of mutations in these pathways, followed by targeted therapy, could be interesting in the future to give rise to personalized therapy in several types of cancers.[11] NSCLC is comprised of three major histological subtypes: squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma.[12]

In this study, we analyzed the characteristics and data of patients with NSCLC lung cancer such as age, sex, pathology, tumor location, metastasis, and also the relationship between EGFR mutation and clinicopathological features in patients hospitalized in the oncology clinic, Kermanshah, Iran.

Patients and Methods

During 2007-2014, 64 patients with NSCLC referred to our clinic in Kermanshah city, Iran. We analyzed sex, age, histopathology, location of the tumor**,** site of metastasis, kind of treatment and overall survival (OS) in all patients. The 3-year OS was calculated as the time from diagnosis to death or last contact. Patients who did not complete the follow-up were excluded from the study. The mean follow-up for the patients was 15 months (range: 3-64 months).

The technique for testing EGFR mutations was FFPE tissue block, including 20% of the tumor. DNA was extracted by FFPE QIAamp kit. EGFR mutations were analyzed by applying DxS kit using Multiplex allele specific real-time PCR×29 primers (ARMS Method) and DxS Scorpion and ARMS assay. These kits could detect the most common (approximately 98%) mutations in the EGFR gene (exons 18-21). The detection limit of this assay is 1% for mutations in wild-type background of DNA.

The correlation between the variables was analyzed by PASW SPSS (version 19) with Chi-square test and T-test, and $P<0.05$ was statistically significant. The curve of the OS was plotted by Kaplan-Meier plot in Graph Pad prism 5 Software in the 3-year period.

Results

Mean±SD age of the patients at diagnosis was 60.02±12.54 years (range: 24-88 years). 51 (79.7%) patients were male and 13 (20.3%) patients were female. 43 (67.2%) patients had distant metastasis. We divided the patients into five age groups, as follows: 2 (3.1%) were 14-39 years old, 9 (14%) were 40-49 years old, 22 (34.3%) were 50-59 years old, 14 (22%) were 60-69 years old, and 17 (26.6%) were older than 70 years (table 1).

Adenocarcinoma, SCC, and large cell carcinoma were the most common histological subtypes in 44 (68.8%), 15 (23.3%), and 5 (7.9%) patients, respectively. The tumor was located in the right lung in 36 (56.2%) patients, in the left lung in 19 (29.7%), and 9 (14.1%) patients showed evidence of tumor in both lungs. 14 (21.9%) patients had early stage and 50 (78.1%) had advanced stage lung cancer. All patients received chemotherapy. 54.7%, 26.6%, and 40.6% were also treated with radiation, maintenance therapy (EGFR tyrosine kinase inhibitors [TKIs] such as Erlotinib) and targeted therapy, respectively. Among 35 patients who were tested for EGFR gene, 26 (74.2%) were mutated while 9 (25.7%) had wild-type. Those who were mutated received EGFR-targeted therapy and were treated with Erlotinib (Tarceva). We found no significant correlation between the variables with EGFR mutation in the patients ($P>0.05$, table 2).

The 3-year OS rate was 25% , while the mean OS was 16 months for all patients (figure 1).

Table 1: The characteristics of patients with non-small cell lung cancer (n=64)

Variables	n (%)
Age group (yrs)	
14-39	2 (3.1)
40-49	9 (14)
50-59	22 (34.3)
60-69	14 (22)
>70	17 (26.6)
Sex	
Male	51 (79.7)
Female	13 (20.3)
Metastasis	
Yes	43 (67.2)
No	21 (32.8)
Site of Metastasis	
Bone	29 (67.4)
Liver	9 (21)
Brain	6 (14)
Lung	4 (9.3)
Histologic Subtype	
Adenocarcinoma	44 (68.8)
SCC	15 (23.3)
Large cell Carcinoma	5 (7.9)
Laterality	
Right	36 (56.2)
Left	19 (29.7)
Both	9 (14.1)
Stage	
Early	26 (40.6)
Advanced	38 (59.4)
Type of Treatment	
Radiation	35(54.7)
Maintenance therapy	17 (26.6)
EGFR-targeted therapy	26 (40.6)
EGFR gene (n=35)	
Mutation	26 (74.2)
Wild-type	9 (25.7)

Discussion

Lung cancer is the most common cause of cancer death worldwide with more than 1.3 million people dying of the disease annually.[13] Approximately 85% of the patients with lung cancer have NSCLC and 40% of these individuals are designated as stage IV metastatic disease at diagnosis.[14] In Kermanshah, the raw and standardized incidence of lung cancer was 3.2 and 6.1 in 100,000 people over 11 years of study (1997-2007). The

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Table 2: The correlation between demographic and histologic variables and EGFR mutation in the patients (n=35)

Variables	EGFR		P value
	Mutation	Wild-type	
Age (mean±SD)	61.1±12.2	54.4±11.9	0.164
Sex			
Male	21	8	0.507
Female	5	1	
Histological Subtype			
Adenocarcinoma	18	7	0.488
SCC≠	8	2	
Tumor Location			
Side of Right 36(56.2)	14	3	0.296
Side of Left	9	3	
Both Sides	3	3	
Metastasis			
Yes	4	4	0.095
No	22	5	
Stage			
Early	9	2	0.403
Advanced	17	7	

**t* test; **Chi-square test; ≠Squamous cell carcinoma

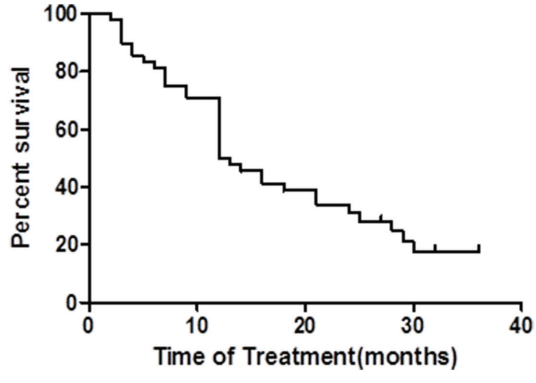

Figure 1: The 3-year overall survival for all patients with non-small cell lung cancer

annual percentage change showed a decrease over the years (3.4% decrease in 100,000 in each year).[15] Table 3 shows the number, age and sex of patients with lung cancer in our study and different areas of Iran. The mean age of patients in Iran and also our study was in the range of 55-65 years with male dominancy.

Adenocarcinoma has been reported as the most common histological subtype of lung cancer in some studies.[8] A study of 2161 patients with lung cancer showed that 55.6% of tumors were adenocarcinoma, 20.5% were SCC, 15% were small cell, 2.7% were large cell and 6.2% comprised other subtypes.[24] In our study, adenocarcinoma and SCC were the most common histological subtypes.

NSCLC is among the most prevalent malignancies and is the major cause of cancer-related deaths worldwide. 20-50% of the patients present with metastatic disease and the most common extrapulmonary sites of distant metastasis are brain, bone, liver, and adrenal gland.[25]

Tamura and colleagues reported that among 729 patients with metastatic NSCLC, 250 (34.3%), 234 (32.1%), 207 (28.4%), 122 (16.7%), 98 (13.4%) and 69 (9.5%) patients had bone, lung, brain, adrenal gland, liver, and extrathoracic lymph node metastasis, respectively.[26] Mordant and co-workers showed that in 94 patients with NSCLC, metastatectomy was performed in 73.4%. Moreover, metastastatic sites included the brain (60.6%), bone (14.9%), adrenal gland (12.8%), skin (6.4%) and liver (5.3%).[27] In our study, 67.2% of the patients had metastasis with the bone, liver, brain, and lung being the most common sites. Another study showed that the sites of the initial failure of NSCLC patients were lung (62.34%), bone (17.72%), central nervous system

Table 3: The characteristics of patients with lung cancer in Iran in different studys

Reference	Iran's province	Number of Patients	Mean age (yrs)	Male (%)	Age range (yrs)
4	Qazvin	203	65.7	81.3	-
16	Yazd	148	63	73	-
17	Mashhad	40	57.2	52	15-65
18	Tehran	242	-	74	-
19	Tehran	40	55.5	80	16-77
20	Tehran	129	67.5	60	-
21	Tehran	242	59.9	73.6	-
22	Tehran	1128	57.86	77	-
23	South	238	56	76	25-65
Our study	Kermanshah	64	60.02	79.7	24-88

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(16.14%), liver (9.49%), and others (7.19%).[28] In our study, metastasis to bone and liver was more common than the other studies which might be attributed to the genetic background or behavior of the tumor; however, these data should be confirmed in future studies in the same geographical regions.

Evaluation for EGFR mutations is now considered to be the standard of care in advanced-stage pulmonary adenocarcinoma and hence, EGFR receptor targeted therapy has become an integral part of the treatment of patients with NSCLC.[29,30] Other studies have reported that the rate of EGFR amplification was not correlated with the age and sex of the patients[30,31] and also histological subtype of the tumor,[30] In our study the results were similar. In another report, EGFR amplification had significant correlation with the stage of the disease; [30] this was not observed in our study.

NSCLC accounts for 85% of all new cases of lung cancer diagnosed around the world; around 40% of these patients were presented with advanced stages.[32] The patients with locally advanced NSCLC who did not receive radical surgery and patients who received concomitant chemotherapy and radiotherapy had a 3-year OS of approximately 27%.[33] Another study reported that the overall 1-, 2- and 3-year survival rates for NSCLC were 28.9, 7.9, and 3.3%, respectively.[34] Most patients either present with advanced disease or develop recurrence at some time during their course of the disease, so that the 5-year survival rate for lung cancer patients was only about 15% and the prognosis of patients with advanced NSCLC is generally considered poor, with a median survival of 8–10 months and a 2-year survival of no more than 10%–20%.[35] Also, Molina and colleagues reported that lung cancer has a dismal 5-year survival rate of 15%.[36] In this study, 59.4% of the patients had advanced stage lung cancer and 3-year OS rate was 25%.

Conclusion

The mean age of Iranian patients with lung cancer was between 55-65 years old. In this study, metastasis to the bone was more common than other studies. Adenocarcinoma of lung still comprises the most common histological subtype. Overall survival in this study was higher. It is noteworthy that there was no association between status of EGFR mutation (wild type vs. mutated) and demographic data, histological type of the tumor or metastatic state of the patients.

Conflict of Interest: None declared.

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