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Epidemiologic and Histopathologic Feature of Lung Cancer in Central Iran (2012-2018)

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Abstract

Background: Lung cancer is one of the common causes of death worldwide. Although the incidence rate of lung cancer in Western countries is decreasing, it presents a growing trend in developed countries. Since there is no accurate enough information about the epidemiological and Histopathologic features of lung cancer in central Iran, Isfahan, we were motivated to conduct this research**.**

Materials and Methods: This was a descriptive, cross-sectional study carried out in central Iran, Isfahan. All demographic, histopathological and clinical data of the lung cancer patients registered in MACSA, a referral charity-based cancer center in central Iran, was analyzed within 2012-2018 using SPSS v.22 software.

Results: Altogether 260 patients with lung cancer were included in this study from 6127 cancer patients registered within 2012-2018 (4.2%). Out of them, 66.2% were men, and 18.8 % of the patients were alive at the time of the study. The mean age of the patients at diagnosis was 61.56 (SD=14.11, range: 9-93). Altogether, 63.1% of patients had metastasis of whom 57.6% were in stage IV at diagnosis. The Frequency of different types of lung cancer was 36.9% adenocarcinomas, 14.2% squamous cell

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carcinoma, 9.6% bronchogenic carcinoma and 8.1% small cell lung cancer, respectively. Altogether, 128 cases were smokers with an average 35.45 ± 14 pack-years. Only in 36.2% of the patients, the diagnostic and therapeutic biomarkers had been checked, and CK7 was positive in 88.9% of the cases in which the biomarker had been checked.

Conclusion: Despite to similar Iranian studies, the most common histopathologic type of lung cancer among the patients was adenocarcinoma that it may be attributed to the lower consumption of smoking in our population and their different genetic context. Molecular biomarkers had been checked in a small portion of the patients. More education of the clinicians along with the development of cancer molecular testing may lead to promote the personalized-based approach.

Key word: lung cancer, Epidemiology, Histopathology, Central Iran, Isfahan

Introduction

Cancer is the second leading cause of death in developed countries and the third one in developing countries like Iran(1,2). The incidence of cancer in developing countries is increasing due to the population aging and the raising of some lifestyle-related cancer risk factors like smoking, physical inactivity, obesity, stress, etc. Cancer is the third most common cause of mortality after cardiovascular disease and car accidents in Iran(3).

Lung cancer is one of the common causes of death worldwide (4). Lung cancer affects more than a million people a year, according to the International Agency for Research on Cancer (IARC). Because of the high mortality rate of lung cancer, scientists pay more attention to its diagnosis, treatment, and prognosis (5). In the United States, lung cancer is the second most common cancer among men and women (6). Moreover, lung cancer is the third most common cancer in both genders with the highest rate of death in Europe (7). Although the incidence rate of lung cancer is estimated low in Iran, its survival rate is not promising (8).

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Lung cancer is usually divided into two groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLCs accounts for about 85% of all lung cancers and are classified into squamous cell carcinoma (SCC), adenocarcinoma (AC), and large cell carcinoma (9). The epidemiology of lung cancer is changing in many parts of the world, as we enter the 21st century. The incidence trend of lung cancer is not promising, however, it moves from developed to less developed countries (10). However, the relationship between smoking and various types of histological findings of lung cancer is not similar, so there is a significant relationship between smoking and the occurrence of SCLC and SCC, but its association with adenocarcinoma is lower (11).

There are Limited epidemiologic studies on lung cancer in Iran. Some studies show that the incidence of lung cancer may be increased by changes in the smoking pattern. The incidence of lung cancer in the North West and West provinces of Iran has been estimated higher than other regions (12). Since there is no accurate enough information about the epidemiological and Histopathologic feature of the lung cancer in central Iran, Isfahan, we were motivated to conduct this research.

Materials and Methods

This was a descriptive, cross-sectional study carried out in Ala cancer control and prevention center (MACSA), a charity-based institute for supportive and palliative care of cancer in central Iran, Isfahan. All the patients registered in MACSA have an electronic database including clinical and para-clinical information. In this study, demographic, histopathological and clinicopathological information of all patients with lung cancer admitted to MACSA was obtained from 2012 to 2018. Demographic variables included age at diagnosis, age at death, gender, and location of living. Moreover, some cancer-related risk factors such as smoking (cigarette, opium or Hookah), alcohol addiction, and chronic contact with chemical substance were also included. Histopathological variables including pathologic feature, metastasis state, the tumor stage, type and size, and the tumor biomarkers were also assessed. Moreover,

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clinicopathological factors containing the first main symptom, past medical history, the family history of cancer and the type of treatment were included. The collected data was analyzed to determine the statistical information and correlations by SPSS v.22 software.

Results

Altogether among 6127 cancer patients registered in MACSA within 2012-2018, 260 patients with lung cancer (4.2%) were included in this study. Out of this population, 172 (66.2%) were men, and 49 (18.8 %) patients were alive at the time of the study. The male to female ratio is 1.95. Overall, 242 patients (93.1%) were urban residents, and the others (6.9%) were rural. The average age of the patients at diagnosis was 60.30 (SD=14.31, 9-93), and at the time of death 62.59 (SD=13.71). Moreover, the mean period time from diagnosis to death was 13.36 (SD=12.31) months.

Out of total lung cancer patients, 135 cases (51.9%) had a positive family history of cancer of whom 92 (68.1%) cases have at-least a first-degree relative with cancer. The most common malignancies among the affected family members were in lung (32, 23.7%), breast (17, 12.6%) and stomach (17, 12.6%), respectively. (Table 1)

Altogether, 164 (63.1%) and 150 (57.6%) patients had metastasis at the time of study and diagnosis, respectively (Table 2). The common sites of metastasis were bone (73, 44.5%), brain (60, 36.6%) and liver (31, 18.9%), respectively.

According to the pathological reports, the Frequency of different types of lung cancer were 96 (36.9%) cases of adenocarcinomas, 37 (14.2%) cases of squamous cell carcinoma, 25 (9.6%) cases of bronchogenic carcinoma and 21 (8.1%) cases of small cell lung cancer, respectively.

The histopathological feature of the studied malignancies were categorized in four types include: 21 SCLC (8.1%), 162 NSCLC (62.3%), 51 cases other types of lung cancer (19.6%) and 26 cases (10%) unknown. In the unknown category the pathological feature of the patients' tumors had not been identified (Table3).Overall, 41% of the tumors were located in the left side, 37.2% in the right side and 16.7% in the bronchi of lung.

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Out of 260 patients, 128 cases (49.2%) were smokers with an average (35.45 ± 14) pack per year.

The exposure rate of the patients with some of the environmental factors investigated in this study listed in Table 4. According to our study, 125 (72.6%) of men and 3 (3.4%) of women were active cigarette smoker.

The most common early symptoms in the patients were cough (209, 80.4%), dyspnea (31, 11.9%), hoarseness (11, 4.2%) and hemoptysis (9, 3.5%), respectively. Moreover, 158 cases (60.8%) had a history of a chronic disease, including 40 (25.3%) patients with ischemic heart disease, 37 (23.4%) with diabetes and 49 (31%) with hypertension.

Also, a history of COPD (Chronic Obstructive Pulmonary Disease), Asthma, and TB (Tuberculosis) has been reported for 4 (1.5 %), 2 (0.8%) and 1(0.4 %) patients, respectively.

Radiation or chemo-procedures for therapeutic or palliative intention had been done for 175 (67.3%) patients of whom 95 patients (54.3%) had tolerated palliative chemotherapy, and 80 patients (45.7%) had received therapeutic chemotherapy. Radiation therapy had been done for 160 patients of whom 99 cases (61.9%) were therapeutic and the others were palliative.

Altogether, 53 molecular biomarkers had been checked by Immunohistochemical (IHC) staining of tumor samples. The most common biomarkers have been listed in Table 5.

Discussion

Epidemiology

Although the incidence rate of lung cancer in Western countries is decreasing, it presents a growing trend in developed countries (13). According to the some previous studies, it seems the incidence rate of lung cancer in Iran is lower than Western countries (6). The national reports have showed that the prevalence of lung cancer is ranked as seventh or eighth among men and above the tenth among women, while on the global scale, it is the first in men and fourth in women (14). This retrospective study was conducted on the 260

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patients with lung cancer out of 6127 cancer patients registered in MACSA within 2012-2018. The aim of this study was to investigate the epidemiological and histoclinicopathological features among the lung cancer patients in central Iran.

According to the previous studies in Iran, male to female ratio has been reported 2.85 (12), 3.22 (15) and 5.09 (16), while in our study it was 1.95. In other countries like Spain and India the ratio was 8.1 (17) and 4.1 (18) respectively. The lower male to female ratio with the lung cancer compared with other countries can be due to difference in environmental exposures of Iranian women, also, some probable genetics variations. Further investigations based on the risk assessment are highly recommended for this population.

In our study, the mean age of the patients at the time of study was 61.5 (SD=14). According to the results of other studies in Iran the mean age of the patients were 65.7 (SD= 11.2) (16), 59.9 (SD= 13) (19) and 64.09 (SD= 9.44) (20). In studies at other countries like India (21) and Canada (22) the mean age of the patients were 56 and 75years respectively .This can be attributed to the different genetic context and environmental and lifestyle-related factors (15). The mean age at time of study among men (61.69, SD=12.84) and women (61.30, SD= 16.39) (P=0.041) were similar to the studies at Tehran (P=0.001, P=0.004)(15,23) and different with study at Qazvin(P=0.171)(16).

Altogether, 51.9% of the patients had a positive family history of cancer (the presence of different cancers among the first or second-degree relatives of the patient) of whom 68.1% were in the first-degree relatives. Studies in Ardebil (west- north of Iran)(20) and Tehran (23)showed the 17.3% and 11.6 % of patients had positive family history of cancer. Additionally, the most common cancers among the family members were lung (23.7%), breast (12.6%) and stomach (12.6%), respectively. In a similar Turkish study,38% of 213 patients had a positive family history of cancer, including 41.9% lung, 19% gastrointestinal, and 7.6% breast cancers(24). Although MACSA is considered as a referral center for cancer patients in central Iran, Isfahan, apparently more evaluations in future studies, with emphasis on the genetic context of the disease could be helpful.

Residence of the patients was 93.1% in urban and 6.9% in rural areas (13.49 times). In one study at Teaching Hospital of Qazvin(Iran)(16), 54.2% of patients and in the study in

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Ardebil(20), 54.1% were urban. Since according to the last study of Statistical Center of Iran, the 85.42% and 14.57% of total population of Isfahan Province were urban and rural, respectively(25), we expect this proportion would be also among the patients with lung cancer if there is no difference between urban and rural populations regarding to the incidence rate of the disease. With comparison the results, it is revealed that the proportion of the urban patients to the rural ones is 13.49, while it is 5.86 in Isfahan general population. It means the incidence rate of the disease in the urban population is estimated 2.3 times more than the rural populations. It may be attributed to the air pollution and other environmental cancer-related risk factors which have been accumulated in the urban regions more than rural areas. More population-based studies can evaluate this hypothesis.

Histopathological features

Overall, 63.1% of the patients had metastasis at the time of study of which 57.6% had presented metastasis at diagnosis. Common metastatic sites were bone, brain, and liver. According to one study in India(26), the rate of lung cancer metastasis was 32.5%. In the study at Tehran(15) 67.3% of patients had metastasis in which the sites included contralateral lung, bone, liver, brain. According to table 2, 57.6% patients were diagnosed in stage 4 and 21.5% in stage 3. In the studies at Tehran(15), 85.3% were in stages 3 to 4, in other study at Tehran(22), 48.5% were in Stage 4, and in the study at Sari(north of Iran) (27), 85.1% of patients were in stage 4.

In most cases of lung cancer, the disease is diagnosed in advanced stages (28). Based on this information the screening program in Iran should be paid more attention to early detection of lung cancers and making biological clues for different sites of metastasis.

According to the pathological reports (Table 3), the frequency of different types of lung cancer were 36.9% cases of adenocarcinomas, 14.2% cases of squamous cell carcinoma, 9.6% cases of bronchogenic carcinoma and 8.1% cases small cell lung cancer, respectively. There was significant relationship between different types of lung cancer and sex ($p<0.001$). (Figure 1)

In the study at Teaching Hospital of Qazvin (Iran)(16), 52.7% of patients had SCC and

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In the study at Yazd(Iran)(8) 34.9% of patients had SCC and In study at Tehran (23), 19% of patients were SCC (Table 6).

According to the results, totally 93 patients (35.7%) had IHC assay reports in which 53 different diagnostic, prognostic, and predictive biomarkers had been measured (Table 5, 7).

Although all of the measured biomarkers have a diagnostic significance (29–34), the most relevant biomarkers which have been recently identified, CK20 and CK7, have an important prognostic value in lung cancer patients(35). Moreover, predictive markers like LCA (31) has been checked in a few patients. It seems, currently, IHC tests for cancer in Iranian patients are requested for diagnostic indications than predictive ones. It may be due to the limitation of cancer molecular and genetic testing facilities in Iran. Apparently, development of new advanced cancer genetic labs along with the education of clinicians towards personalized medicine-associated approaches on cancer could promote the clinical applications of molecular cancer biomarkers in Iran.

Environmental risk factors

Smoking, is the most important lung cancer-related risk factor, so 90-85% of all lung cancers are directly caused by exposure to cigarettes (36) . In our study, 49.2% of the patients were cigarette smokers with an average 35.45 (SD= 14) pack per year. In other studies at Tehran, 57.2% (15) and 72.9%(23) and in study at Ardebil(north of Iran) (20), 90.8% were cigarette smokers with an average 25.7 (SD= 38.67) pack per year. It seems other environmental factors are suspected as the underlying cause of catching lung cancer in the patients. So, we investigated other factors according to table 4, hookah smoking, opium addiction and alcohol consumption, as the other potential reasons for catching lung cancer in the studied population. On the other hand, 125 (72.6%) of men and 3 (3.4%) of women were active cigarette smokers and there is a significant difference between sexes and cigarette smoking, hookah smoking, opium addiction and alcohol consumption ($p<0.001$). In the study at Tehran(15), 70.3% of male and 5% of female lung cancer patients were cigarette smoker. This difference is likely due to the less consumption of cigarettes among Iranian women because of the cultural reason when we compare with the other countries (23). Accordingly, we expect the male to female

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proportion among the Iranian patients with lung cancer be significantly more than other countries with high prevalence of smoking among their women. This proportion, however, is less than other countries, according to our results and their comparison with other foreign studies(17,18). It could be referred to the different genetic background in our populations in comparison to the other countries and more effect of the inheritable genetic factors in pathogenesis of the disease. This conclusion may be approved by the high prevalence of familial lung cancer among the patients compared to other populations, an issue which needs more evaluations in the next studies.

In other studies of Iranian population like Teaching Hospital of Qazvin (Iran)(16), 17.2% of the patients had opium addiction, 47.4% baking bread history, 2.4 % contact with a chemical substance. In one study at Ardebil(20), 34.7% had opium addiction and 11.3% had a history of baking bread. Totally our study suggests, instead of concentrating on cigarette consumption between lung cancer patients, we should pay more attention to the other ways of smoking (hookah and opium) and environmental exposures in Iranian patients to achieve comprehensive risk factors underlying lung cancer.

According to other studies, smoking is associated with a higher proportion of SCC. The lower prevalence of SCC in our study may be due to the lower consumption of cigarettes in the population than other populations studied in Iran. There was, also, a significant difference in the histopathologic type of lung cancer ($p<0.001$) between sexes in this study, similar to other Iranian studies (15,16,23).

Due to the limitations of our study (inaccessibility to the other risk factors and comprehensive molecular study), we could not conclude any other items.

Clinical aspects

According to the results, the most common early symptoms of lung cancer among the patients were cough and dyspnea. In the Qazvin study (16), 76.5% patients had cough as an early symptom but in the Ardebil study (20) the most common symptom was hemoptysis (32.7%). This controversy in studies needs more comprehensive data to make an accurate decision about the early symptoms of lung cancer in Iranian patients. Altogether, 67.3% patients had a history of chemotherapy and 38.1% had a history of radiation therapy. In one study at Sari (north of Iran)(27), 57% of the patients had

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tolerated chemotherapy. These results may be correlated to the stage of diagnosis in our patients. Curative chemotherapy and radiotherapy are more acceptable for the patients who are not in the advanced stage.

Conclusion

This study was performed on 260 patients with lung cancer who had been referred to MACSA-Isfahan within 2012-2018. The prevalence of disease was significantly more in men and in urban patients.

There was a significant difference between the mean age of women and men with lung cancer. Most of the patients had metastasis at the time of referral and bones were the most common site of metastasis. There was a significant relationship between sex and smoking. The most common histopathologic feature of lung cancer among the patients was adenocarcinoma, probably due to the lower consumption of smoking in our population. In some patients, the diagnostic and therapeutic biomarkers had been checked, and CK7 was positive in most of the cases in which the biomarker was checked. Given the limitations of this study regarding the accessibility of the patients' data and sample size, more investigations are recommended to reveal a more accurate epidemiologic and clinicohistopathologic feature of the disease and its risk factors in central Iran.

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Tables and Figures

Table 1: The site of cancers among the family members of the patients with lung cancer registered in MACSA-Isfahan within 2012-2018

The site of cancer	Frequency of affected members	Percent (percent in total 260 patients)	Valid percent (percent in total 135 patients)
Lung	32	12.3	23.7
Breast	17	6.5	12.6
Stomach	17	6.5	12.6
Colorectal	13	5.2	9.1
Brain	12	4.6	8.9
Hematopoietic tract	12	4.8	8.4
Liver	10	3.8	7.4
Prostate	10	3.8	7.4
Small Intestine	9	3.5	6.7
Uterine	7	2.7	5.2
Skin	6	2.4	4.2
Larynx	4	1.5	3.0
Pancreas	4	1.5	3.0
Esophagus	2	0.8	1.5
MUO	1	0.4	0.7
Kidney	1	0.4	0.7
Testis	1	0.4	0.7
Salivary glands	1	0.4	0.7

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Table 2: The Frequency of histopathological TNM tumor stage at the time of diagnosis in the patients with lung cancer registered in MACSA-Isfahan within 2012-2018

TNM tumor stage	Frequency	Percent
stage 4	150	57.6
stage 3	56	21.5
stage 2	43	16.5
stage 1	11	4.2
Total	260	100.0

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Table 3: The frequency of different histopathological types of lung cancer in the patients with lung cancer registered in MACSA-Isfahan within 2012-2018

SCC: Squamous Cell Carcinoma

SCLC: Small cell lung cancer

NSCLC: Non-small cell lung cancer

histopathological type	Frequency	Percent
Adenocarcinoma[1]	96	36.9
SCC[1]	37	14.2
unknown[4]	26	10.0
Bronchogenic carcinoma[3]	25	9.6
SCLC[2]	21	8.1
Sarcomatoid carcinoma[1]	18	6.9
Neuroendocrine carcinoma[3]	12	4.6
Mesotheliuma[3]	11	4.2
NSCLC[1]	9	3.5
Lymphoma[3]	3	1.2
Large cell carcinoma[1]	2	.8
Total	260	100.0

1: NSCLC 2: SCLC 3: Other types of lung cancer 4: Unknown

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Table 4: The exposure rate with some of the environmental factors in the patients with lung cancer registered in MACSA-Isfahan within 2012-2018

SCLC: Small cell lung cancer
NSCLC: Non-small cell lung cancer

Risk Factor	NSCLC	SCLC	Other	Un known	Total number (%)
Cigarette smoking	68 (52.7%)	14 (73.6%)	40 (46.5%)	6 (23.0%)	128(49.2%)
Passive smoker	23 (17.8%)	2 (10.52%)	19 (22.09%)	7 (26.92%)	51(19.61%)
Hookah smoking	52 (40.3%)	12 (63.1%)	33 (38.37%)	4 (15.38%)	101(38.8%)
Opium addiction	40 (31%)	8 (42.1%)	17 (19.76%)	1 (3.84%)	66(25.38%)
Alcoholic drinker	9 (6.97%)	0	3 (3.48%)	1 (3.84%)	13(5%)
Cooking bread	11 (8.52%)	0	7 (8.1%)	3 (11.53%)	21(8%)
Carpet weaving	12 (9.30%)	0	9 (10.4%)	2 (7.69%)	23(8.84%)
Chemical substance	23 (17.82 %)	3 (15.7%)	16 (18.6%)	2 (7.69%)	44(16.92%)
Asbestosis	1 (0.77%)	0	1 (1.16%)	0	2(0.7%)
Total	129	19	86	26	

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Table 5: The frequency distribution of the lung cancer patients according to the molecular biomarkers checked on their tumor samples

valid	Frequency		Biomarker frequency unavailable data	Percent of positive	Valid percent of positive
	positive	negative			
CK7	48	6	206	18.5	88.9
TTF1	42	17	201	16.2	71.2
PR	0	3	257	0	0
CK5	4	3	253	1.5	57.1
CK20	11	37	212	4.2	22.9
CD56	0	8	252	0	0
CD19	0	1	259	0	0
CD20	3	9	248	1.2	25.0
CD3	2	4	254	0.8	33.3
CD7	0	1	259	0	0
CD33	1	0	259	0.4	100.0
CD68	1	0	259	0.4	100.0
AE1/AE3	1	0	259	0.4	100.0
TG	0	1	259	0	0
CD99	5	1	254	1.9	83.3
CALRETININ	4	14	242	1.5	22.2
CD34	2	1	257	0.8	66.7
S100	2	4	254	0.8	33.3
DESMIN	2	4	254	0.8	33.3
BCL2	2	1	257	0.8	66.7
CD117	1	3	256	0.4	25.0
CYTOCERATIN7/20	0	1	259	0	0
NSE	5	0	255	1.9	100.0

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EMA	3	2	255	1.2	60.0
CYTOCIN20	1	0	259	0.4	100.0
GCDFP15	0	2	258	0	0
CD10	1	1	258	0.4	50.0
CK6	4	4	252	1.5	50.0
CA125	0	4	256	0	0
ALK1	0	1	259	0	0
EGFR	2	2	256	0.8	50.0
CD5	1	3	256	0.4	25.0
TDT	1	1	258	0.4	50.0
WT1	2	10	248	0.8	16.7
CEA	5	6	249	1.9	45.5
GATA3	1	4	255	0.4	20.0
VIMENTIN	6	6	248	2.3	50.0
CHOROMOGRANIN	13	7	240	5.0	65.0
SYNAPTOPHYSIN	15	4	241	5.8	78.9
P63	9	7	244	3.5	56.3
CDX2	1	18	241	0.4	5.3
CK	21	7	232	8.1	75.0
CK8	1	0	259	0.4	100.0
CK18	1	0	259	0.4	100.0
ER	1	7	252	0.4	12.5
CD56	2	0	258	0.8	100.0
GFAP	0	1	259	0	0
LCA	4	11	245	1.5	26.7
NAPSINE	5	1	254	1.9	83.3
PSA	0	3	257	0	0
SMA	1	0	259	0.4	100.0
MELAN A	0	1	259	0	0

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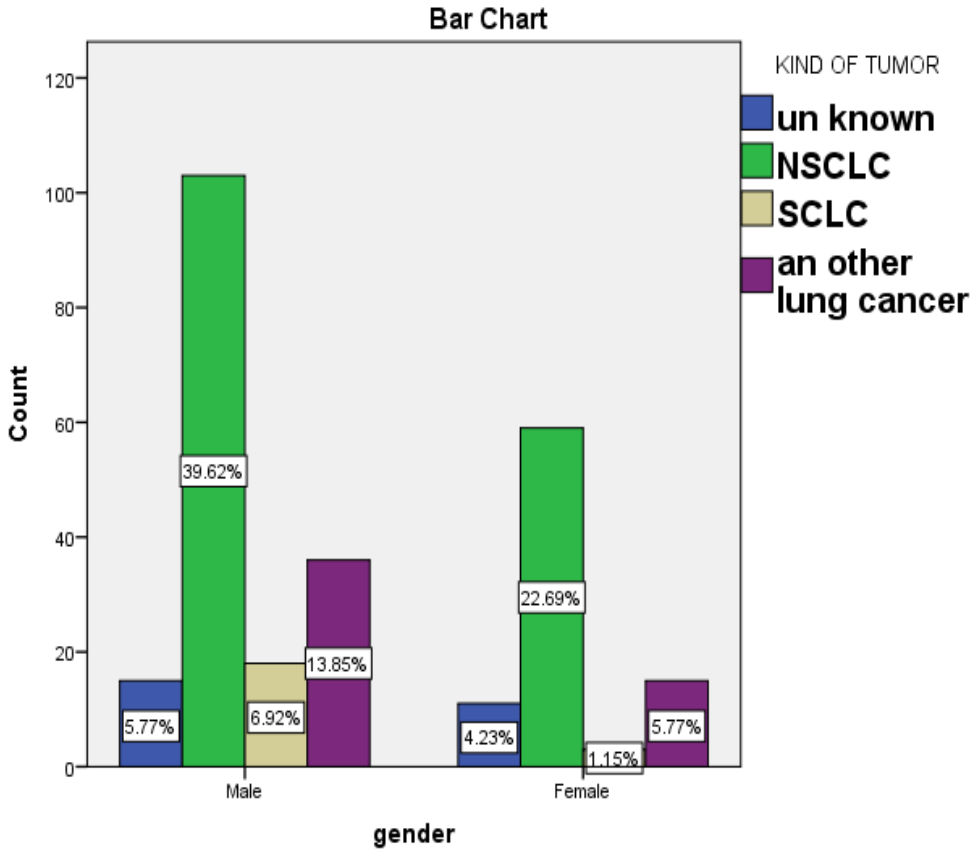

Figure 1: The frequency distribution of different types of lung cancer according to the sex, in the patients registered in MACSA-Isfahan within 2012-2018

SCLC: Small cell lung cancer
NSCLC: Non-small cell lung cancer

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Table 6: The frequency of histopathologic types of lung cancer in the current study and other similar studies in Iran.

histopathologic type	Current study	Tehran study(15)	Ardebil study(20)	Tehran study(23)	Qazvin study(16)	Yazd study(8)
Adenocarcinoma (AC)	36.9%	45.01%	14.5%	28.9%	14.8%	23.5%
Squamous cell carcinoma(SCC)	14.2%	23.28%	61.3%	19%	52.7%	34.9%
Small cell lung cancer(SCLC)	8.1%	16.93%	16.9%	18.6%	13.3%	22%

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Table 7: The most relevant biomarkers that have been checked in the patients with lung cancer registered in MACSA-Isfahan within 2012-2018

Biomarker	Total number of checked biomarker (percent in total 93 Patients)	Number of Positive (percent)	Number of Negative(percent)
CK20*&**	60(64.5%)	14(23.3%)	46(76.6%)
TTF1*	59(63.4%)	42(71.1%)	17(28.8%)
CK7*&**	54(58%)	48(88.8%)	6(11.1%)
CK5/6*	28(30.1%)	21(75%)	7(25%)
Chromogranin*	20(21.5%)	13(65%)	7(35%)
Synaptophysin*	19(20.4%)	15(78.9%)	4(21%)
CDX2*	19(20.4%)	1(5.2%)	18(94.7%)
Calretinin*	18(19.3%)	4(22.2%)	14(77.7%)
P63*	16(17.2%)	9(56.2%)	7(43.7%)
LCA***	15(16.1%)	4(26.6%)	11(73.3%)
VIMENTIN**	12(12.9%)	6(50%)	6(50%)
WT1**	12(12.9%)	2(16.6%)	10(83.3%)
CEA**	11(11.8%)	5(45.4%)	6(54.5%)

*the diagnostic biomarkers. **the prognostic biomarkers. ***the predictive biomarkers. (29, 33, 36, 37)