

## Gender and age trends of histological types of lung cancer in a 20-year period: pathological perspective

J. Stojsic<sup>1</sup>, J. Radojicic<sup>1</sup>, J. Markovic<sup>1</sup>, B. Milenkovic<sup>1</sup>, D. Maric<sup>1</sup>, T. Adzic<sup>1</sup>, I. Milovanovic<sup>2</sup>

<sup>1</sup>Institute for Pulmonary Diseases and Tuberculosis, Clinical Center of Serbia, Belgrade; <sup>2</sup>Institute of Pathophysiology, School of Medicine, University of Belgrade, Serbia

### Summary

**Purpose:** To find out the trends of distribution in different histological types of lung cancer in both genders in a period of 20 years.

**Methods:** The most frequent histological types of lung cancer in tissue specimens obtained by bronchoscopy or percutaneous needle biopsy were analysed in terms of age and gender. The studied population included 6289 patients (16.6% females and 83.1% males). Statistical significance was established by  $\chi^2$  test at the level  $p < 0.05$ .

**Results:** Squamous cell carcinoma (SCC) prevailed in

the total number of patients in all investigated years (58.0%), and separately in male (60.4%) and female (45.7%) patients. This histological type was predominant in all age groups in both genders (41.6% in males and 38.1% in females).

**Conclusion:** SCC has the highest incidence in Serbia. Continuous campaign against smoking and helping its cessation, improving working and socioeconomic conditions is a strategy for decreasing all histological types of lung cancer patients.

**Key words:** lung cancer, biopsy, trends of histological types

### Introduction

Lung cancer is the most frequently diagnosed malignant disease all over the world. In men, it is the first cause of mortality and in women it is on the third place, just after breast and colorectal cancer but before cervical cancer [1-3]. Good preventive measures and early detection of breast and cervical cancers will probably put lung cancer as the leading cause of mortality in women worldwide [4]. In Serbia, lung cancer is a malignancy with high rate of morbidity and mortality in both genders [5-7].

The aim of this study was to retrospectively analyse the distribution of the most frequent histological types of lung cancer in both genders, together and separately, and their age, from 1985 to 2005. The obtained results were compared with those available from the relevant literature concerning neighboring to Serbia countries and in various parts of the world too.

### Methods

Pulmonary bioptic tissue specimens were sampled from patients of both genders by bronchoscopy or percutaneous needle biopsy. Analysis was based on histological diagnosis of the primary lung cancer made on routine histological examination collected from pathological reports from the Department of Pathology, Institute for Lung Diseases and Tuberculosis, Clinical Centre Serbia, Belgrade, as referral institution for lung diseases for Belgrade and Central Serbia.

Lung cancer was classified according to World Health Organization (WHO) 2004 classification into 3 major types: squamous cell carcinoma (SCC), small cell lung carcinoma (SCLC) and adenocarcinoma (AC). Other, rarer pulmonary malignancies such as adenosquamous cancer, large cell and sarcomatoid lung cancer, carcinoid tumors and salivary gland tumors were included in a separate 4th group [1]. The age of patients

was divided into 10-year increment groups, from 0-10 to > 90 years.

Differences were analysed using  $\chi^2$  test and the statistical significance of differences was put at  $p < 0.05$ .

## Results

Lung cancer diagnosis was established in 6289 patients (16.6% females and 83.4% males; M/F ratio 5:1). In 1985 and 1995 this ratio was 6.3:1 and 6.5:1 but in 2005 decreased to 3.1:1. SCC was the predominant histological type in the 20-year period (58%), in male (60.4%) and female (45.7%) patients. Detailed data regarding the other major histological types are shown in Table 1.

Also, in the same period SCC was the predominant histological type, up to 67.4% in 1990, in the total number of patients. The distribution of histological types of lung cancer in the investigated years are shown in Table 2.

SCC was also the dominant histological type of lung cancer in all age groups and in both genders. Detailed data are displayed in Table 3.

Statistically significant difference in the distribution of SCC to SCLC, AC and the other rarer malignant lung tumors was noted (58.0%, 24.5%, 15.5% and 2.0%, respectively;  $p = 0.0001$ ) in both genders and all age groups.

Lung cancer was most frequently diagnosed in

women aged 61-70 years (34.7%). The majority of SCC was diagnosed in 180 (38.1%) women in that decade of life. SCC was the predominant histological type of lung cancer in all age groups and in both genders. Similarly to males, there was statistical significance between SCC, SCLC, AC and the other rarer malignant lung tumors (45.7%, 28.2%, 22.2% and 3.9% respectively;  $p = 0.002$ ). The histological distribution of lung cancer with regard to age in females is shown in Table 4.

Table 5 displays the distribution of lung cancer histologies in males in relation to age. Three histological types (SCC, SCLC and AC) were most frequently diagnosed (40%) in the 51-60 age group in male patients, while the rarer histological types were diagnosed in 35.4% of patients of the 61-70 age group. There was significant difference between SCC and the other histological types (60.4%, 25.1%, 12.9% and 1.6%, respectively;  $p = 0.0001$ ).

## Discussion

In annual reports of the Central Register for Cancer in Belgrade and central Serbia, lung cancer incidence in males is in the first and in females in the third place [7]. Lung cancer ranks first in males and the second in females in the northern region of Serbia, Vojvodina [8]. In Bulgaria lung cancer is expected to rise until 2017 in both genders [9]. Lung cancer incidence in Slovenia is the prevailing malignancy in male and third in

**Table 1.** Lung cancer diagnosis in both genders

Gender	SCC		SCLC		AC		Other		Total	
	N	%	N	%	N	%	N	%	N	%
Male	3171	60.4	1315	25.1	679	12.9	82	1.6	5247	83.4
Female	476	45.7	231	22.2	294	28.2	41	3.9	1042	16.6
Total	3647	58.0	1546	24.5	973	15.5	123	2.0	6289	100.0

SCC: squamous cell carcinoma, SCLC: small cell lung cancer, AC: adenocarcinoma, Other: rare pulmonary malignancies

**Table 2.** Year distribution of histological types of lung cancer in both genders

Year	SCC		SCLC		AC		Other		Total	
	N	%	N	%	N	%	N	%	N	%
1985	528	57.1	275	29.8	81	8.8	40	4.3	924	14.7
1990	1118	67.4	357	21.5	161	9.7	23	1.4	1659	26.4
1995	608	51.0	391	32.8	173	14.5	20	1.7	1192	19.0
2000	825	52.7	345	22.1	381	24.4	13	0.8	1564	24.9
2005	568	59.8	178	18.7	177	18.6	27	2.8	950	15.0
Total	3647	58.0	1546	24.5	973	15.5	18	2.0	6289	100.0

For abbreviations see footnote of Table 1

**Table 3.** Age distribution of histological types of lung cancer in both genders

Histological type	Age grouping																Total	
	1		2		3		4		5		6		7		8		N	%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SCC	1	0.1	53	1.5	418	11.5	1455	39.9	1316	36.1	372	10.2	22	0.6	1	0.1	3647	58.0
SCLC	0	0	50	3.1	199	12.7	645	41.9	490	31.8	156	10.1	6	0.4	0	0	1546	24.5
AC	5	0.5	19	2.00	154	15.8	304	31.2	330	34.0	156	16.0	5	0.5	0	0	973	15.5
Other	4	3.3	11	8.9	18	14.6	35	28.5	43	35.0	11	8.9	1	0.8	0	0	123	2.0
Total	10	0.2	133	2.1	789	12.5	2439	38.8	2179	34.6	695	11.1	34	0.5	1	0.1	6289	100.0

Age grouping (years): 1 = up to 30, 2 = 31-40, 3 = 41-50, 4 = 51-60, 5 = 61-70, 6 = 71-80, 7 = 81-90, 8 = over 90

For abbreviations see foot of Table 1

**Table 4.** Distribution of lung cancer according to histological type and age in female patients

Histological type	Age grouping																Total	
	1		2		3		4		5		6		7		8		N	%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SCC	0	0	16	3.4	83	17.6	139	29.1	180	38.1	50	10.3	8	1.5	0	0	476	45.7
SCLC	0	0	6	3.1	26	11.2	104	44.8	66	28.4	28	12.1	1	0.4	0	0	231	22.2
AC	3	1.0	8	2.7	51	17.5	88	29.7	103	35.0	41	14.1	0	0	0	0	294	28.2
Others	1	2.3	6	13.6	7	18.2	9	22.7	14	31.8	4	11.4	0	0	0	0	41	3.9
Total	4	0.4	37	3.6	170	16.3	338	32.4	362	34.7	123	11.8	8	0.8	0	0	1042	100.0

For abbreviations and age grouping see footnote of Tables 1 and 3

**Table 5.** Distribution of lung cancer according to histological type and age in male patients

Histological type	Age grouping																Total	
	1		2		3		4		5		6		7		8		N	%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SCC	1	0.1	38	1.2	338	10.6	1318	41.6	1138	35.8	323	10.2	14	0.4	1	0.1	3171	60.4
SCLC	0	0	44	3.3	173	13.2	541	41.1	424	32.2	128	9.7	5	0.5	0	0	1315	25.1
AC	2	0.4	11	1.6	103	15.2	216	31.8	227	33.4	115	16.9	5	0.7	0	0	679	12.9
Other	3	3.7	5	6.1	11	13.4	26	31.7	29	35.4	7	8.5	1	1.2	0	0	82	1.6
Total	6	0.3	98	1.9	625	11.9	2101	40.0	1818	34.6	573	10.9	25	0.5	1	0.1	5247	100.0

For abbreviations and age grouping see footnote of Tables 1 and 3

female population [10]. The same incidence was found in Croatia for both genders in the period from 1993 to 1997 [11]. However, all these reports do not contain distribution data regarding the histological types of lung cancer.

The female/male ratio was 3.8 in 1979 and decreased to 1.6 in 1998 in Canada, according to Alberta Cancer Registry [12]. The same situation was found in the Connecticut study in the period from 1960 to 1964 (female/male ratio was 6.5 and decreased to 2.1 in the period from 1985 to 1989) [13]. In our study in 1985 and 1995 this ratio was 6.3 and 6.5, but in 2005 it decreased to 3.1.

The results of this study were compared with those of other studies where the histological types of lung cancer were confirmed by biopsy. In recent years, AC replaced SCC as the most frequent histology for both sexes

and all races combined [14]. The National Cancer Institute in Bethesda, USA, provides statistical information of lung and the other carcinomas from 1975 to 2005. In both genders the incidence of lung cancer is most frequent between 70 to 79 years of age in all races. AC is the most frequent in female (40.4%) and male (33.3%) patients and in both genders together (36.6%), while SCC is less frequent in female (15.7%), male (23.8%) and in the total number of patients (20.1%) [15]. In Alberta Cancer Registry AC predominated in female (32%) and SCC in male patients (32%) from 1979 to 1998 [12]. In a report from the Connecticut Tumor Registry from 1960 to 1989, increasing incidence of SCC and SCLC in male and AC in female patients was noted [13]. According to Swedish Family-Cancer Database in the period from 1958 to 1996, SCC and AC accounted for 35.1% and 16.8% among males.

AC (35.1%) was more frequent than SCC (17.7%) among females. SCC in males decreased slightly from a peak in the 1980s, while in females it increased steadily. The incidence of AC increased in both genders [16]. Polish investigators found, based on community-based cancer registry, that AC is predominant in female and male non-smokers (26.4% and 5.6%, respectively), while in smokers of both genders SCC is the prevailing histological type (73.6% and 94.4%, respectively) [17]. SCC is the most frequent histological type of lung cancer in the majority of countries of the African continent [18]. According to World Health Organization data, SCC is the most frequent in male (44.0%) and AC in female (42%) patients in Africa [1]. In the largest south American country, Brasil, according to one hospital-based study, the mean patients' age with lung cancer at diagnosis was 64 years in men and 59 years in women. The prevalence of smoking was 97.36% among men (around 52 packs/years), and 72.97% among women (33 packs/years). Histologically, SCC prevailed (37.5%), followed by AC (30%) [19]. Lung cancer incidence in Australian population is the highest in both genders, higher than melanoma incidence [11].

Our results have shown that SCC is the most frequent histological type (45.7% in female, 60.4% in male, and 58.0% in the total number of lung cancer patients). AC was diagnosed in 28.2% in female, 12.9% in male and 15.5% in the total number of lung cancer patients. Considering age distribution lung cancer was most frequent between 61 to 70 years of age.

Smoking is the major risk factor of SCC, as well as air pollutants in urban environment and poor working conditions [20-25]. In Serbia smoking in women is 3-fold higher compared to the world's average. Smoking is more frequent in urban than in rural areas [26]. This could possibly explain why SCC was more frequent than AC in both genders in our investigation.

Viral infections, especially human papillomavirus (HPV), may be a possible risk factor of lung cancer. This virus is known to cause cervical cancer, but according to one recent study, it may be the cause of lung cancer in non-smoking women in whom this virus was recovered from the tracheobronchial tree [20].

Studies on the effect of tobacco smoking to AC development are controversial. AC develops in secondary or passive smokers and filter or light cigarette smokers mostly used by women according to studies from western and middle European and far East countries. Diminished hormonal activity in menopause also influenced lung cancer development in women according to some studies. Higher estrogen serum level and hormone replacement therapy increased the risk for developing lung cancer, especially if associated with tobacco smoking. Early menopause was associated with a decreased risk, particularly

of AC [17,27,28]. In a 10-year hospital-based study, an association of lung cancer, especially AC (51.2%), with connective tissue diseases was found. According to that investigation, female patients with connective tissue diseases were affected by lung cancer more frequently than male patients (96%) [29]. Healthy diet, particularly the consumption of fresh fruits and vegetables, reduces the risk of lung cancer, especially in non-smokers [20,30].

In our research the increased number of diagnosed AC could be explained in several ways. First, is that AC is usually a peripheral pulmonary tumor, more accessible to percutaneous needle and transbronchial biopsy, hence more easy to histological diagnosis in comparison with other histologies [14]. Second, could be that histological diagnosis has been improved by the introduction of immunohistochemical tissue staining methods making it possible to differentiate poorly differentiated SCC from solid, poorly differentiated AC, in the last two investigated years (2000 and 2005).

SCLC was mostly seen in the 51-60 years age group in our study. Similar results were reported in an investigation from Turkey where the authors' opinion was that socioeconomic conditions, inadequate nutrition and poor living conditions might have affected the development of this histological type of lung cancer [31]. In a second study from Turkey, SCLC was predominant in patients younger than 50 years [32]. Serbia was in bad socioeconomic condition during the wars in the former Yugoslavia in the last decade of the 20th century when the peak of SCLC was observed.

The increasing number of patients affected by other rarer lung cancer types could be attributed to improved histological diagnosis due to wide application of immunohistochemistry stainings in the later years of this investigation.

The authors' opinion is that the highest frequency of SCC appears in undeveloped and less developed countries, while AC is more frequent in developed countries. A reason for the observed high frequency of SCC in undeveloped or less developed countries could be attributed to inadequate strategy in the prevention and cessation of smoking, especially among youngsters. Long exposure to pollutants in working and living places, particularly in urban environment, is the leading cause of the high incidence of SCC in both genders and in all ages. Improved socioeconomic conditions, healthy nutrition and hormonal balance are important for the prevention of lung cancer development in both genders.

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