

Histological Types and Age Distribution of Lung Cancer Operated Patients over a 20-year Period: A Pathohistological Based Study

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SUMMARY

Introduction Lung cancer is the leading cause of death from malignancy in Serbia.

Objective This is a retrospective analysis of lung cancer epidemiological changes regarding to its histological type and patients' age of both genders. Data were based on surgically treated lung cancer patients from 1985 to 2005.

Methods Data were collected from 972 pathohistological reports of operated patients of both genders divided into age groups. Histological types of lung cancer were distributed in four major groups: squamous cell cancer (SCC), adenocarcinoma (AC), small cell cancer (SCLC) and other rare histological types. Both genders together and separately were analysed. Chi-square with the level of significance $p < 0.05$ and chi-square test for trends were used as statistical methods.

Results SCC predominated in both genders; in 44.7% females and 68.0% males. AC was less frequently diagnosed (21.8%) than SCC (64.0%) in both genders and all age groups. The most frequently operated patients were aged between 51 and 60 years (36.6%) with SCC and AC predominance. Three patients with SCLC were operated in 61-70 age-group. In age-group up to 30 years, three (0.5%) patients were operated on for SCC and other rare lung tumours, respectively. Predominance of other rare lung tumours was established in 51-60 age-group, 25% of patients of both genders.

Conclusion SCC is the most frequent histological type of lung cancer found in all age groups and in both genders of surgically treated patients.

Keywords: lung cancer; histological type; surgery; gender; age

INTRODUCTION

Many published reports refer to the distribution of predominant histological type of lung cancer and patient's age and gender on tissue samples obtained by lung biopsy [1-5]. Lung cancer is identified as the major health problem among malignancies in Serbia [6]. This malignancy ranks the first in males and the second in females in Serbia [7, 8].

We did not find any report in the relevant literature with analysis of histological type and age distribution of operated lung cancer patients.

OBJECTIVE

This analysis represents pathohistological point of view on changes in epidemiology of lung cancer due to its histological type and patients' age of both genders. It is based on surgically treated lung cancer patients in the period of 20 years, from 1985 to 2005. We compared these

results with those obtained on biopsy specimens during the same period.

METHODS

Data were collected from pathohistological reports performed at the Department of Thoracopulmonary Pathology of the Service of Pathology, Clinical Centre of Serbia. Pathohistological diagnosis was established by one or two pathologists. Different opinions or difficulties in establishing the pathological diagnosis by both pathologists were resolved by immunohistochemistry.

Recent 2004 World Health Organization (WHO) lung cancer classification was used in the analysis. Lung cancer was classified into three major histological types: squamous cell carcinoma (SCC), small cell lung carcinoma (SCLC) and adenocarcinoma (AC). The 4th histological type included other rare pulmonary malignancies: adenosquamous, large cell- and sarcomatoid lung cancers, carcinoid and

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salivary gland tumours [9]. The age of patients was divided into ten-year old age-groups, except the first group, which included patients aged from 0 to 30 years.

The changes of epidemiological findings of histological types of lung cancer were determined every 5 years, with the beginning in 1985 up to 2005.

For processed data distribution and analysis we used descriptive statistical method, chi-square test with level of significance $p < 0.05$ and chi-square test for trends. Data were analysed using software package SPSS for Windows, version 10.0.

RESULTS

Analysis was made of 972 pathohistologically diagnosed lung cancers; 17.5% females and 82.5% males. The average male/female ratio was 4.9. This ratio was higher in 1990 and 2005 (5.3 and 5.1) than in 1985 and 1995 (4.1 and 4.9) and in 2000 it was 4.9. SCC was predominant in both genders; 44.7% females and 67.1% males. Distribution of all histological types of lung cancer is presented in Table 1. Statistical difference was found between SCC and AC, SCLC and other lung tumours in both genders (63.2% versus 3.8%, 27.0% and 6.1%, respectively; $p = 0.001$).

AC was less frequently diagnosed (262) than SCC (614) in both genders and in all investigated years. Increasing trends for all histological types, except for other rare histological types were evident in both genders and are presented in Graph 1. $Y_{SCC} = -15513 + 7.84x$; $r^2 = 0.71$;

Table 1. Histological types of operated patients of both genders

Histological type	Gender		Total	
	Female	Male		
SCC	N	76	538	614
	%	44.7	67.1	63.2
AC	N	69	193	262
	%	40.6	24.1	27.0
SCLC	N	7	30	37
	%	4.1	3.7	3.8
Other	N	18	41	59
	%	10.6	5.1	6.1
Total	N	170	802	972
	%	17.5	82.5	100.0

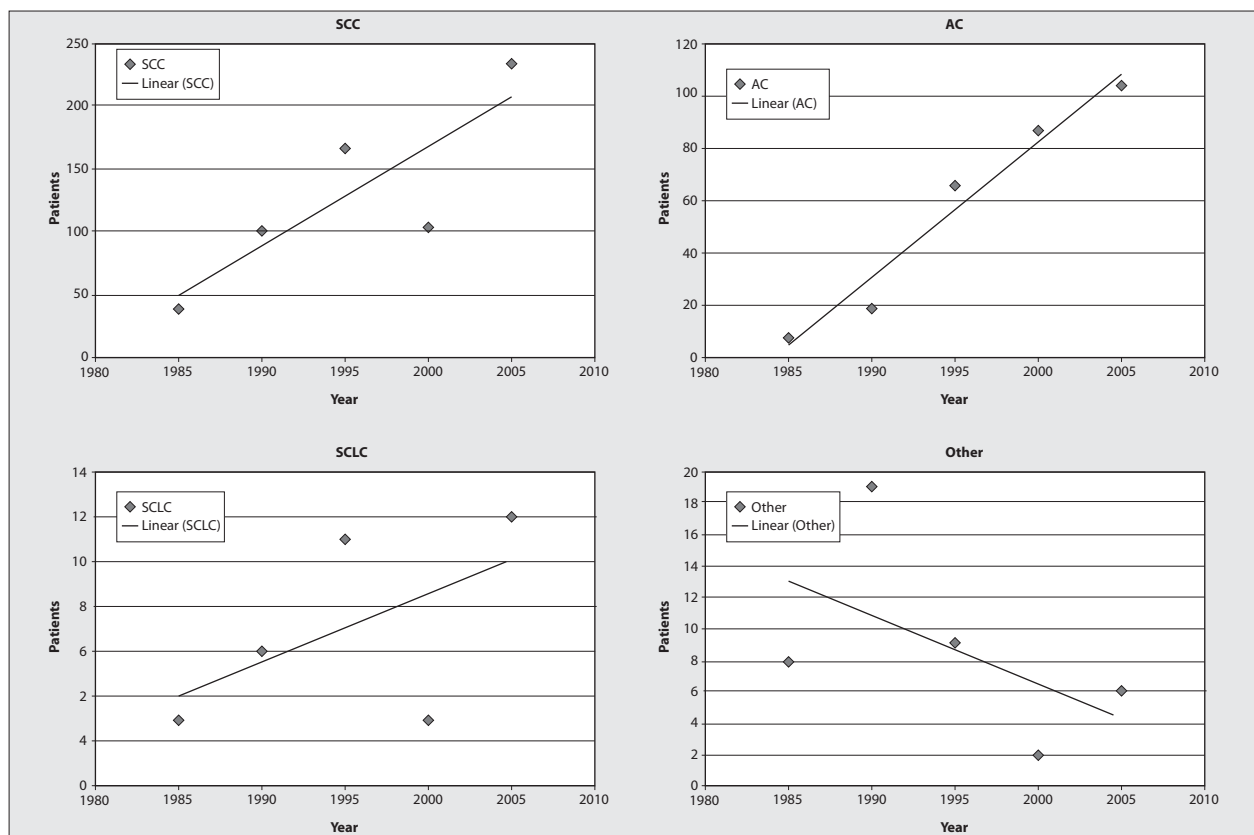
N – number of patients; AC – adenocarcinoma; SCLC – small cell carcinoma; SCC – squamous cell carcinoma

$Y_{AC} = -10278.1 + 5.18x$; $r^2 = 0.96$; $Y_{SCLC} = -591.5 + 0.3x$; $r^2 = 0.3$;
 $Y_{Other} = 846.7 - 0.42x$; $r^2 = 0.28$.

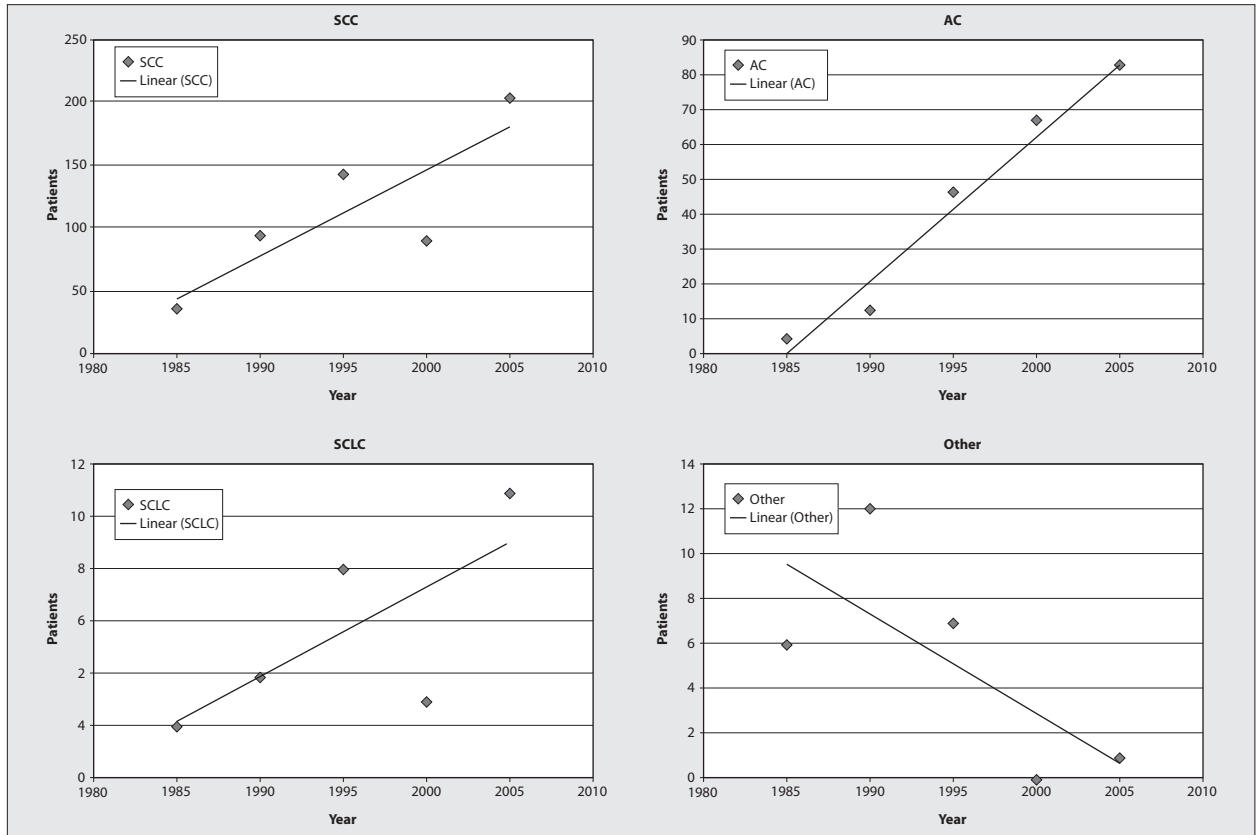
The same trends were present in male patients and are shown in Graph 2. $Y_{SCC} = -2179.3 + 1.1x$; $r^2 = 0.68$; $Y_{AC} = -1901.4 + 0.96x$; $r^2 = 0.86$; $Y_{SCLC} = 81.2 - 0.4x$; $r^2 = 0.08$; $Y_{Other} = -36.3 + 0.02x$; $r^2 = 0.00$.

Among female patients the increasing trends of SCC and AC were noted. Contrary to male patients, SCLC trend decreased and for other rare histological types it increased. The trends are presented in Graph 3. $Y_{SCC} = -13333.7 + 6.74x$; $r^2 = 0.7$; $Y_{AC} = -8376.7 + 4.22x$; $r^2 = 0.97$; $Y_{SCLC} = -672.7 + 0.34x$; $r^2 = 0.51$; $Y_{Other} = 883.0 - 0.44x$; $r^2 = 0.51$.

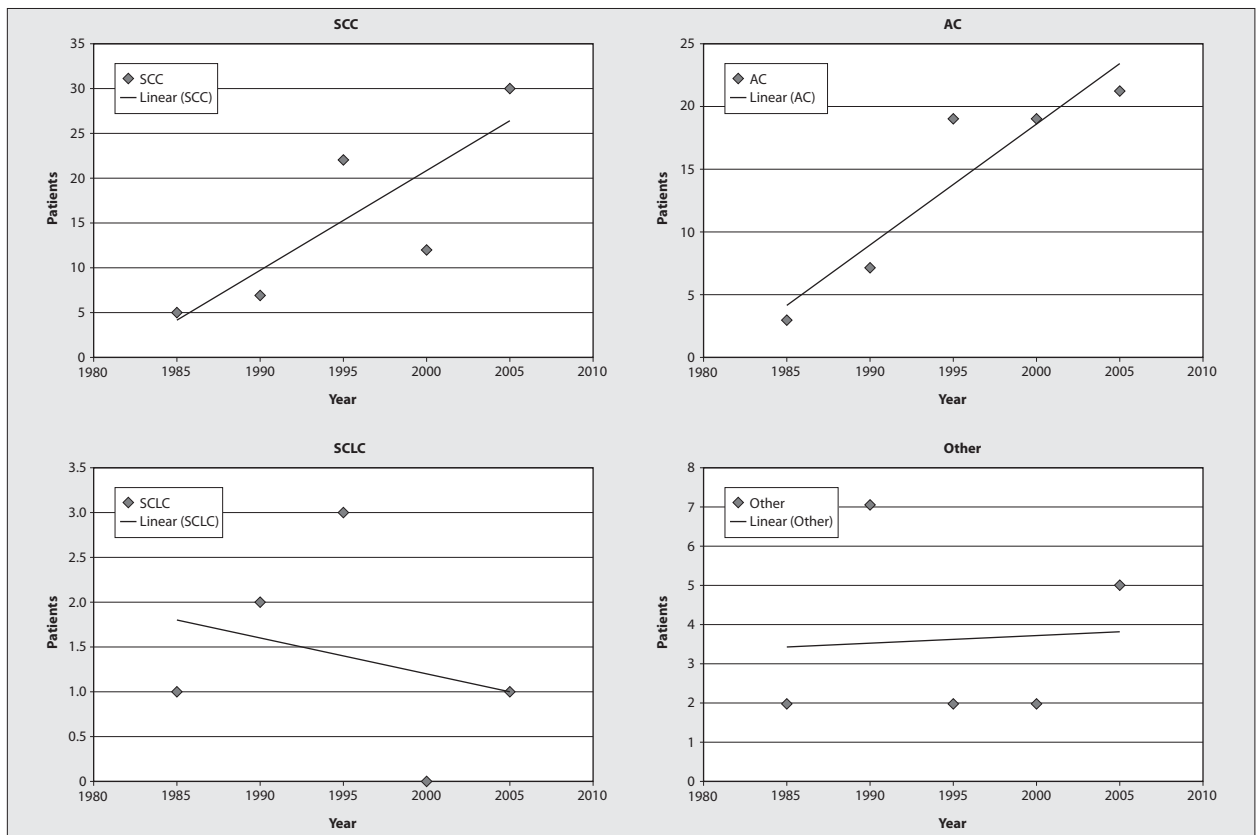
Distribution of four major histological types of tissue samples regarding the age of lung operated cancer patients



Graph 1. Trends of four major histological types of lung cancer in both genders over 20-year period



Graph 2. Trends of four major histological types of lung cancer in males over 20-year period



Graph 3. Trends of four major histological types of lung cancer in females over 20-year period

of both genders totally and separately was analysed. Among 972 patients of both genders, 40.1% were registered between 51 and 60 years of age. All major histological types predominated in this age group. SCC predominated in all age groups except in those aged up to 30 years. There was a statistical significance in age distribution of operatively treated patients of both genders (40.1% versus 29.2%, 19.9%, 6.1%, 4.1% and 0.6%, respectively; $p=0.0001$). The detailed data are presented in Table 2.

There was a statistical significance in age distribution of male patients (41.0% versus 29.7%, 19.1%, 6.1%, 3.5% and 0.6%, respectively; $p=0.0001$). The most frequently operated patients were aged between 51 and 60 years. SCC predominated in all, except in age-group up to 30 years (three patients). Details are presented in Table 3.

In operated females there was no statistical significance in age distribution (60%, 46%, 27.1%, 24.1%, 7.0%, 5.9% and 0.6%, respectively; $p=0.389$). AC predominated only in age groups between 51-60 years. SCC predominated in all other age groups. Detailed distribution of histological types of lung cancer regarding female patients' age could be seen in Table 4.

DISCUSSION

The majority of studies contained four groups of histological types of lung cancer, SCC, AC, SCLC and other rare epithelial malignancy [1-5]. However, we did not find any relevant published report about its distribution based

exclusively on samples obtained by pneumonectomy, lobectomy or wedge resection. Reported results were compared with ours, which were obtained by bronchoscopy and lung percutaneous needle biopsy in the same period of investigation. In a previously published report about the distribution of major histological types of lung cancer on biopsies, SCC was predominant in both genders and age groups and in all investigated years for the same period. The only difference was found in female patients who underwent biopsy because predominant distribution was detected in a 61-70 age-group [10]. The predominance of SCC (86.6%) was found in one Serbian study of surgically treated septuagenarian patients [11].

Smoking is the major risk factor for developing SCC, as well as air noxae in urban environment and poor working conditions in both genders. Cigarette smoking among women in Serbia is 3-fold more frequent as compared to that of the world average. Women smokers are rarely consumers of filter low tar cigarettes which involves AC in our country [1, 2, 12-18]. One explanation for AC increase could be better pathohistological diagnosis applying immunohistochemistry, particularly in the differentiation of poorly differentiated SCC from solid poorly differentiated AC. The second explanation is that AC, as a peripheral pulmonary tumour, is more frequently resectable than SCC which is mostly a central tumour mass [9].

The worldwide increasing number of AC operated patients could be explained by the use of video assisted thoracic surgery (VATS) as a safe method even among older patients. VATS is more useful in surgery of AC, which is

Table 2. Distribution of lung cancer according to the histological type and age on surgery in patients of both age

Histological type	Age (years)													
	≤30		31-40		41-50		51-60		61-70		71-80		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SCC	3	0.5	23	3.7	122	19.9	224	36.5	200	32.6	42	6.8	614	63.1
AC	0	0	7	2.7	50	19.1	126	48.1	65	24.8	14	5.3	262	27
SCLC	0	0	2	5.4	4	10.8	19	51.4	9	24.3	3	8.1	37	3.8
Other	3	0.5	8	13.6	17	28.8	21	35.6	10	16.9	0	0	59	6.1
Total	6	0.6	40	4.1	193	19.9	390	40.1	284	29.2	59	6.1	972	100

Table 3. Distribution of lung cancer according to the histological type and age on surgery in males

Histological type	Age (years)													
	≤30		31-40		41-50		51-60		61-70		71-80		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SCC	2	0.4	18	3.3	105	19.	201	37.4	177	32.9	35	6.5	538	67.1
AC	0	0	3	1.6	35	18.1	97	50.3	46	23.8	12	6.2	193	24.1
SCLC	0	0	1	3.3	4	13.3	15	50.0	8	26.7	2	6.7	30	3.7
Other	3	7.3	6	14.6	9	18.1	16	39.0	7	17.1	0	0	41	5.1
Total	5	0.6	28	3.5	153	19.1	329	41.0	238	29.7	49	6.1	802	100

Table 4. Distribution of lung cancer according to the histological type and age on surgery in females

Histological type	Age (years)													
	≤30		31-40		41-50		51-60		61-70		71-80		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
SCC	1	1.3	5	6.6	17	22.4	23	30.3	23	30.3	7	9.2	76	44.7
AC	0	0	4	5.8	15	21.7	29	42.0	19	27.5	2	2.9	69	40.6
SCLC	0	0	1	14.3	1	14.3	3	42.9	1	14.3	1	14.3	7	4.1
Other	0	0	2	11.1	8	44.4	5	27.8	3	16.7	0	0	18	10.6
Total	1	0.6	12	7.0	41	24.1	60	35.3	46	27.1	10	5.9	170	100

located more frequently as peripheral lung tumour [19, 20, 21]. Lung AC could be resected in patients with various connective tissue diseases [22]. There is an increasing tendency for AC mostly in the developed countries and in female population, in all on account of SCC which develops more often in the undeveloped countries and in male population [23-27].

SCLC treatment is by chemotherapy or in combination with radiotherapy. Peripherally localized SCLC could be treated surgically mostly in cases where preoperative diagnosis was not established or in cases where SCLC was misdiagnosed particularly with small cell type SCC confirmed by preoperative biopsy without immunohistochemistry.

A higher number of patients affected by other rare lung cancers, mostly carcinoid tumours, is due to improved pathohistological diagnosis applying immunohistochemistry. The increasing number of surgically treated rare histological types of lung cancers, such as carcinoids and salivary tumours, is explained by their lower aggressiveness and higher operability and resectability [28]. In our study these tumours were diagnosed in younger age groups.

CONCLUSION

Increasing tendency of all histological type could be explained with increasing number of lung cancer surgeries performed in both genders during the total studied period. SCC is the most frequent histological type diagnosed in surgically treated lung tumours with predominance in both genders and in all age groups. The same results were obtained in a previous study based on bronchoscopy and percutaneous needle biopsy findings. This could explain why SCC is more frequently operated than AC, except in female patients aged between 51-60 years. SCLC was surgically treated mostly in preoperatively misdiagnosed cases. Other lung tumours, mostly carcinoid tumours were diagnosed frequently in younger age groups. A more precise preoperative diagnosis of these tumours, particularly by applying immunohistochemistry, and their lower aggressiveness and better operability was the reason of their frequency unrelated to gender. The majority of operated patients belonged to the age group with the highest frequency of diagnosed lung cancer obtained by biopsy. It was the expected result.

REFERENCES

- Janssen-Heijnen M, Coebergh JW. The changing epidemiology in Europe. *Lung Cancer*. 2003; 41(3):245-58.
- Ringer G, Smith JM, Engel AM, Hendv MP, Lang J. Influence of sex on lung cancer histology, stage and survival in a midwest United States tumor registry. *Clin Lung Cancer*. 2005; 7(3):180-2.
- Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest*. 2003; 123(1 Suppl):215-49S.
- Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer Incidence in Five Continents Volume VIII*. IARC Scientific Publications No. 155. Lyon: International Agency for Research on Cancer; 2002.
- Page GP, Green JL, Lackland D. Epidemiology of lung cancer with specific reference to genetics, bioassay, women, and developing countries. *Semin Respir Crit Care Med*. 2000; 21(5):365-73.
- Janković S, Vlajinac H, Bjegović V, Marinković J, Šipetić-Grujičić S, Marković-Denić Lj, et al. The burden of disease and injury in Serbia. *Eur J Public Health*. 2007; 17(1):80-5.
- Petrović V, Miladinov-Mikov M, Mandić A. Lung cancer trends in Vojvodina. *J BUON*. 2006; 11:49-53.
- Vukicevic A, Miljuš D, Živković S, Mickovski N, Rakočević I, Plavšić P, editor. *Cancer incidence and mortality in central Serbia. Cancer registry of central Serbia, Reports 1, 2 and 3*. Belgrade: Institute of Public Health of Serbia; 2002, 2004 and 2005 (in Serbian).
- Travis WD, Brambilla E, Konrad Müller-Hermelink, Harris CC, editors. *World Health Organisation Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press International Agency for Research on Cancer; 2004.
- Stojisic J, Radojicic J, Markovic J, Milenkovic B, Maric D, Adzic T, et al. Gender and age trends of histological types of lung cancer in a 20-year period – pathological perspective. *J BUON*. 2010; 15(1):136-40.
- Subotic D, Mandaric D, Radosavljevic G, Stojisic J, Gajic M. Lung function changes and complications after lobectomy for lung cancer in septuagenarians. *Ann Thorac Med*. 2009; 4(2):54-9.
- Gazdar AF, Thun MJ. Lung cancer, smoke exposure and sex. *J Clin Oncol*. 2007; 25(5):469-71.
- Lee CH, Ko YC, Goggins W, Huang JJ, Huang MS, Kao EL, et al. Lifetime environmental exposure to tobacco smoke and primary lung cancer of non-smoking Taiwanese women. *Int J Epidemiol*. 2000; 29:224-31.
- Bosetti C, Levi E, Lucchini F, Negri E, Vecchia CL. Lung cancer mortality in European women: recent trends and perspective. *Ann Oncol*. 2005; 16(10):1597-604.
- Thomas L, Doyle LA, Edelman MJ. Lung cancer in women. Emerging differences in epidemiology, biology, and therapy. *Chest*. 2005; 128:370-81.
- Parkin DM, Ferlay J, Hamdi-Cherif M, Sitas F, Thomas J, Wabinga H, et al. *Cancer in Africa: Epidemiology and Prevention*. IARC Scientific Publications No. 153. Lyon: IARC Press; 2003.
- Pesut D, Basara HZ. Cigarette smoking and lung cancer trends in Serbia – a ten-year analysis. *Med Pregl*. 2006; 59(5-6):225-9.
- Stojisic J, Milovanovic I, Radojicic J, Milenkovic B. Lung cancer in women: histological type and patient age from 1985 to 2005. *Med Oncol*. 2009; 26(3):265-8.
- Koike T, Togashi K, Shirato T, Sato S, Hirahara H, Sugawara M, et al. Limited resection for noninvasive bronchioloalveolar carcinoma diagnosed by intraoperative pathologic examination. *Ann Thorac Surg*. 2009; 88(4):1106-11.
- Gharagzloo F, Margolis M, Tempesta B. Robot-assisted thoracoscopic lobectomy for early-stage lung cancer. *Ann Thorac Surg*. 2008; 85(6):1880-5.
- Igai H, Takahashi M, Ohata K, Yamashina A, Matsuoka T, Kameyama K, et al. Surgical treatment for non-small cell lung cancer in octogenarians – the usefulness of video-assisted thoracic surgery. *Interact Cardiovasc Thorac Surg*. 2009; 9:274-7.
- Adzic TN, Pesut DP, Nagorni-Obradovic LM, Stojisic JM, Vasiljevic MD, Bouros D. Clinical features of lung cancer in patients with connective tissue diseases: a 10-year hospital based study. *Respir Med*. 2008; 102(4):620-4.
- Fu JB, Ying Kau T, Severson RK, Kalemkerian GP. Lung cancer in women: analysis of national surveillance, epidemiology and end results database. *Chest*. 2005; 127:768-77.
- Hatcher J, Dover DC. Trends in histopathology of lung cancer in Alberta. *Can J Public Health*. 2003; 94(4):292-6.
- Zheng T, Holford TR, Boyle P, Chen Y, Ward BA, Flannery J, et al. Time trend and the age-period-cohort effect on the incidence of histological types of lung cancer in Connecticut 1960-1989. *Cancer*. 1994; 174(5):1556-67.
- Li X, Mutanen P, Hemminki K. Gender-specific incidence trends in lung cancer by histological type in Sweden, 1958-1996. *Eur J Cancer Prev*. 2001; 10(3):227-35.
- Novaes FT, Cataneo DC, Ruiz Junior RL, Defaveri J, Michelin OC, Cataneo AJ. Lung cancer: histology, staging, treatment and survival. *J Bras Pneumol*. 2008; 34(8):595-600.
- De Perrot M, Licker M, Bouchardy C, Usel M, Robert J, Spiliopoulos A. Sex differences in presentation, management, and prognosis of patients with non-small cell lung carcinoma. *J Thorac Cardiovasc Surg*. 2000; 119:21-6.

Расподела карцинома плућа према хистолошком типу тумора и старости оперисаних болесника током двадесетогодишњег периода – патохистолошка студија

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КРАТАК САДРЖАЈ

Увод Од свих малигнитета карцином плућа је водећи узрок смрти у Србији.

Циљ рада Циљ овог ретроспективног истраживања био је да се утврди расподела карцинома плућа према хистолошком типу тумора, полу и старости болесника.

Методе рада Анализирани су подаци о болесницима који су хируршки лечени због карцинома плућа у периоду 1985–2005. године. Подаци су прикупљени из 972 патохистолошка извештаја оперисаних болесника оба пола, груписаних према старосном добу. Хистолошки типови карцинома плућа подељени су на четири главна: сквамозелуларни карцином (SCC), аденокарцином (AC), ситноћелијски тип (SCLC) и остале, ређе хистолошке типове. Расподела карцинома плућа извршена је према хистолошком типу тумора, полу

и старости болесника. За статистичку обраду добијених резултата коришћен је χ^2 -тест са нивоом значајности $p < 0,05$.

Резултати SCC је био најчешћи тип карцинома плућа, а дијагностикован је код 44,7% жена и 68,0% мушкараца. AC је био ређи, а забележен је код 21,8% болесника, док је SCC утврђен код 64,0%. Највећи број болесника оперисан је између 51. и 60. године (36,6%). Три болесника са SCLC била су оперисана у седмој декади живота. У групи болесника млађих од 30 година по три (0,5%) су била оперисана од SCC и ретких тумора плућа. Ретки тумори плућа утврђени су код болесника оба пола старости од 50 до 60 година (25%).

Закључак SCC је најчешћи хистолошки тип карцинома плућа код оперисаних болесника у свим старосним групама.

Кључне речи: карцином плућа; хистолошки тип; операција; пол; старост