

## SMOKING BEHAVIORS AND LUNG CANCER EPIDEMIOLOGY: A COHORT STUDY

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### SUMMARY

**Background:** Lung cancer is the most common cancer in the world. According to the latest available data, in the year 2012 Croatia was among 20 countries with the highest incidence of lung cancer. Although tobacco smoking is a proven cause of lung cancer, recent data show that more than one quarter of adult inhabitants of Croatia are everyday smokers. The purpose of this study was to present epidemiology and treatment modalities of lung cancer in the Department for mediastinal tumors, Clinic for lung diseases Jordanovac, and to make a comparison between the available data from Croatia and the rest of the world.

**Subjects and methods:** The study cohort included 212 newly diagnosed lung cancer patients who had referred to our Department from January 2012 until December 2012. Features such as age, gender, cytology and histology of the tumor, stage at diagnosis and applied therapy were evaluated respectively.

**Results:** Approximately two-thirds of all newly diagnosed lung cancers occurred in men. Out of the study cohort, 12.3% were diagnosed with small cell lung cancer (SCLC) and 87.7% were diagnosed with non-small cell lung cancer (NSCLC). The majority of the patients diagnosed with NSCLC had adenocarcinoma (47.9%), followed by squamous cell carcinoma (33.9%) and large cell carcinoma (15%). Only a small number of patients diagnosed and treated for lung cancer in our Department had never smoked tobacco. The majority of those patients were women and the most common histological type found was adenocarcinoma.

**Conclusion:** The number of patients who had potentially operable disease at presentation was around 10%. That is why, in most cases, therapeutic options were confined to palliative chemotherapy or radiotherapy. Attention should be directed to an early detection of lung cancer patients, which could provide better treatment options and improve overall survival.

**Key words:** lung cancer - lung cancer epidemiology - tobacco smoking - lung cancer treatment

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### INTRODUCTION

Lung cancer is the most common cancer in the world. In the year 2012 there were 1.8 million new cases diagnosed (Ferlay 2012). The same year, Croatia was among 20 countries with the highest incidence of lung cancer, with the world age-standardized rates as high as 34.3 per 100,000 persons (Ferlay 2012). There was an increase compared to the year 2011, when the world age-standardized rate was 33.3 per 100,000 persons. According to the latest data available from the Croatian National Cancer Registry, in the year 2011 in Croatia, lung cancer was the most common solid tumor in men with the incidence rate of 104.1/100,000 persons and the second most common tumor in women with the incidence rate of 34.6/100,000 persons (Croatian National Cancer Registry 2013). Tobacco smoking and exposure to environmental tobacco smoke is a proven cause of lung cancer (Hackshaw et al. 1997, Vineis et al. 2004, IARC 2004), responsible for the development of approximately 85% to 90% of all lung cancers (National Comprehensive Cancer Network 2014). Recent data show that more than one quarter of adult inhabitants of Croatia are everyday smokers, which presents a great public health problem (Kovačić et al. 2007, Samardžić et al. 2009). Approximately 95% of all lung cancers are classified as either small cell lung cancer

(SCLC) or non-small cell lung cancer (NSCLC). There are three main subtypes of NSCLC, including squamous cell carcinoma accounting for about 25% of all lung cancers, adenocarcinoma accounting for about 40%, and large cell carcinoma for about 10% of all lung cancers. About 10% to 15% of all lung cancers are small cell lung cancers. The distribution of NSCLC subtypes is changing. In the last 30 years the incidence of squamous cell carcinoma has been declining while adenocarcinoma has become more frequent (Devesa et al. 2005). The majority of patients present with locally advanced or metastatic disease at the time of diagnosis (stage IIIb or stage IV). Survival rates vary depending on the stage at diagnosis. The median survival time for patients with untreated metastatic NSCLC is 4 to 5 months, with a survival rate at one year of only 10% (Rapp & Pater 1988). Chemotherapy combinations showed a response rate of 19–32% and a median survival time of 7.9 to 11.3 months (Schiller & Harrington. 2002, Fossella & Pereira 2003, Čučević et al. 2005).

The purpose of this study was to present epidemiology and treatment modalities of lung cancer in the Department for mediastinal tumors, Clinic for lung diseases Jordanovac, and to make a comparison between the available data from Croatia and the rest of the world.

## SUBJECTS AND METHODS

The study cohort included all newly diagnosed lung cancer patients who had referred to the Department for mediastinal tumors, Clinic for lung diseases Jordanovac, University Hospital Center Zagreb, from January 2012 until December 2012. In the observed period there were 212 patients diagnosed and treated for lung cancer. Features such as age, gender, cytology and histology of the tumor, stage at diagnosis and applied therapy were evaluated respectively. Cytology and histology data were analyzed according to the World Health Organization (WHO) histological classification (Table 1).

**Table 1.** Patients and tumor characteristics

Characteristic	N	Percentage
Gender		
Male	153	72.2
Female	59	27.8
Age	65; 37-85	
Histology		
NSCLC	186	87.7
SCLC	26	12.3
NSCLC		
Adenocarcinoma	89	47.9
Squamous cell	63	33.9
Large cell	28	15.0
Other types	6	3.2
Tobacco users		
Smokers	182	85.8
Non-smokers	30	14.2

N – number of patients; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer

Radiologic methods used to assess the disease were contrast-enhanced computed tomography scan of chest and upper abdomen, positron emission tomography for evaluation of preoperative treatment, brain imaging and bone scan for clinical suspicion of metastatic disease. Tumor staging was recorded according to the current seventh edition of tumor node metastasis (TNM) classification by The International Association for the Study of Lung cancer (IASLC) (Table 2). Treatment was carried out according to the latest National Guidelines. The first line of treatment for NSCLC stage I, II, and IIIA was surgery (lobectomy, or pulmectomy and lymph node dissection) alone or followed by chemotherapy. The patients who were not willing to accept the procedure-related risk or could not undergo surgery due to co-morbidities, received radio and chemotherapy. Treatment of locally advanced or metastatic disease was based on cisplatin regimens delivered alone or concurrently with radiotherapy. The patients who were not fit for concurrent treatment received chemotherapy alone or with radiotherapy in non-concurrent schedule (Pignon & Stewart 1996). In metastatic or locally advanced disease, platinum was combined with gemcitabine, taxanes and etoposide as the first line chemotherapy (Schiller et al.

2002, Ardizzoni et al. 2007). The patients who had clinical or radiological progression during or after the first line of treatment, received, when possible, pemetrexed or docetaxel as mono-therapy (Di Maio et al. 2009, Hanna et al. 2004). Erlotinib was applied as mono-therapy (Shepherd et al. 2005), when possible, to the patients who had radiological proof of progression on the second line of treatment. The collected data were correlated with Department data from the year 2011 and the available literature data.

**Table 2.** TNM classification

Staging	N	Percentage
Ia	2	0.9
Ib	3	1.4
IIa	2	0.9
IIb	4	1.9
IIIa	13	6.2
IIIb	31	14.6
IV	157	74.1
All stages	212	100.0

N – number of patients

## RESULTS

Out of 212 patients with lung cancer, 153 were male (72.2%) and 59 female (27.8%). The mean age at the time of diagnosis was 65 years, ranging from 37 to 85 years. Out of all the newly diagnosed patients, 26 of them (12.3%) were diagnosed with SCLC and 186 of them (87.7%) were diagnosed with NSCLC. The majority of the patients diagnosed with NSCLC had adenocarcinoma (47.9%), followed by squamous cell carcinoma (33.9%), and large cell carcinoma (15%). Other subtypes were found in 3.2% of the cases. A significant number of the patients (182 of them, 85.8%) were former or active smokers. In the group of the patients who were non-smokers, most of them were diagnosed with adenocarcinoma (22 patients, 73.3%), while the others had squamous cell carcinoma (3 patients, 10%), small cell carcinoma (3 of them, 10%) and large cell carcinoma (2 patients, 6.4%). The majority of the patients in the non-smoking group were women (70%). Only 24 patients (11.3%) were diagnosed with potentially operable disease, all of which had NSCLC, while 188 patients (88.7%) had an advanced stage of disease (IIIB, IV) at the time of diagnosis. Out of the potentially operable patients, 22 (10.4%) were sent to a curative operation procedure (Table 3). Altogether 91 patients (42.9%) had brain or bone metastases, or a locally advanced tumor and received radiotherapy at some point during the treatment (Table 4). Out of all the study population, 159 patients (75%) received some type of chemotherapeutic regimen. As many as 53 patients did not receive chemotherapy due to bad ECOG performance status, co-morbidity or refusal of further treatment. In the SCLC group, 21 patients received platinum-based doublet with etoposide in the first line of

**Table 3.** Surgical treatment of NSCLC

Stage of disease	N	Neo-adjuvant chemotherapy	Adjuvant chemotherapy	Lob/pulm with LND
Ia	2	/	/	2
Ib	3	/	1	3
IIa	2	/	2	2
IIb	4	1	3	4
IIIa	13	8	11	11

N – number of patients; Lob/pulm – lobectomy/pulmectomy; LND – mediastinal lymph node dissection

**Table 4.** Radiotherapeutic regime

Location	N	Percentage
CNS	34	37.4
Gamma-knife	6	
WBRT	28	
Lung and mediastinum	31	34.1
Concurrent C/R	15	
Non-concurrent C/R	16	
Bones	26	28.5

N – number of patients; CNS – central nervous system; WBRT – Whole brain radiotherapy; C/R – chemotherapy/radiotherapy

**Table 5.** Therapeutic regime for SCLC

Therapeutic regime	LoT	Chemotherapeutic option	N.C.	N	Percentage
Operation				/	
BSC				5	19.2
RT				13	50.0
Chemotherapy	First	PE	3.8	21	80.8
		Topotecan	3	5	19.2
	Second	PE	2.7	7	26.9

N – number of patients; LoT – line of treatment; BSC – best supportive care; N.C. – average number of cycles; RT- radiotherapy; PE – cisplatinum or carboplatinum plus etoposide

**Table 6.** Therapeutic regime of NSCLC

Therapeutic regime	LoT	Chemotherapeutic option	N.C.	N	Percentage
Operation		Neo-adjuvant and/or adjuvant		22	11.8
BSC				31	16.7
RT				78	41.9
Chemotherapy	First			138	74.2
		PE	3.6	60	
		GC	3.7	31	
		Taxol/C	3.6	47	
				56	30.0
				8	
	Second	PE	2.9	8	
		GC	4.2	5	
		Pemetrexed	2.5	20	
		Docetaxel	2.8	18	
		Taxol/C	3.6	5	
				31	16.7
				2	
Third	PE	3.5	2		
	Erlotinib	6.3	29		

N – number of patients; LoT – line of treatment; BSC – best supportive care; N.C. – average number of cycles; RT- radiotherapy; PE – cisplatinum or carboplatinum plus etoposid; GC – cisplatinum or carboplatinum + gemcitabine; Taxol/C – cisplatinum or carboplatinum + paclitaxel

chemotherapy and 13 patients received radiotherapy. After registered radiological progression, 13 patients were fit to receive the second line chemotherapy, which included either platinum based regimen or topotecan as mono-therapy (Table 5). In the NSCLC group, 138 patients (74.2%) received chemotherapy and 78 patients (41.9%) received radiotherapy. All the patients in the NSCLC group received platinum-based chemotherapy doublets in the first line of treatment. Carboplatinum or cisplatinum were combined with etoposide (43.5%), gemcitabin (22.5%), or paclitaxel (34%). Out of the patients who had progression during or after the first line, 30% were able to receive the second line of treatment. The majority of the patients (35.6%) received pemetrexed as mono-therapy in the second line of treatment, followed by different types of platinum-based doublets (32.2% patients), or docetaxel as mono-therapy (32.2% patients). Only 16.7% of the patients received the third line of treatment due to further progression; 93.5% of them received erlotinib and only 6.5% received platinum with etoposide (Table 6).

## DISCUSSION

The data collected in this study show that approximately two-thirds of all newly diagnosed lung cancers occurred in men. A similar ratio of the incidence of lung cancer in men and women was observed in the year 2011 in our Department (72% men, 28% women). This is in concordance with the data from the Croatian National Cancer Registry for the year 2011, according to which, out of 2,920 newly diagnosed lung cancer patients, 2,152 (73.7%) were men. In comparison with the data of the previous years in Croatia, the incidence of lung cancer in men fluctuates around the same value and the incidence in women is increasing. Using the world age standardized rates (ASR) for lung cancer incidence, cancer rates for lung cancer in Croatian men are still three times higher than in women, while in developed countries the rate difference is significantly lower (developed countries ASR for men 44.7, for women 19.6/Croatia ASR for men 58.2, for women 15.4). Based on the GLOBOCAN 2008 (developed countries ASR for men 47.4, for women 18.6), it seems that in developed countries the incidence of lung cancer in men decreased while the incidence in women slightly increased. A plausible explanation for this could be found in fierce anti-smoking campaigns that reduce the number of active smokers in developed countries. The situation in Croatia is troubling because there is no overall decline in the number of smokers and the number of women who smoke is growing. Analyses show that only a small number of patients diagnosed and treated for lung cancer in our department have never smoked tobacco. In accordance with the previous findings, the majority of those patients were women and the most common histological type found was adenocarcinoma (Couraud et al. 2012).

The number of newly diagnosed patients admitted to our Department in 2012, who had potentially operable disease at presentation, was around 10%. That is why, in most cases, therapeutic options were confined to palliative chemo or radiotherapy. Current data estimate the number of patients with potentially operable, early stage disease at initial diagnoses to be around 20-30% of all newly diagnosed lung cancer patients (Mauguen et al. 2013, Ellise & Vandermeer 2011, Little et al. 2005). Survival rates vary depending on the stage of the disease, emphasizing the need for an early diagnosis. Current National Comprehensive Cancer Network (NCCN) Guidelines recommend annual lung cancer screening with low dose computed tomography (LDCT) for individuals with the following risk factors: age 55 to 74 years, 30 or more pack year history of smoking tobacco, and current smokers or, if former smokers, have quit within 15 years. For now there is no National Screening Program for lung cancer in Croatia. The distribution of histological types was almost the same as in the year 2011.

Chemotherapeutic treatment was applied in accordance with the latest guidelines whenever it was feasible. Due to the poor general condition at the time of diagnosis, a lot of patients could not receive recommended treatment protocols. Only a handful of patients were able to receive the third line of chemotherapy. Previous studies showed that an early initiation of targeted therapy in the designated patients improves their outcome. European Society for Medical Oncology (ESMO) has already included the prescription of TKIs as the first line treatment to patients with tumors bearing an activating EGFR mutation (Peters et al. 2012). The question of an early detection of patients who are carriers of the epidermal growth factor receptor (EGFR) mutations, proper to receive tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib as the first or second line of chemotherapy, should be considered.

## CONCLUSION

Lung cancer is still one of the leading causes of cancer morbidity and mortality in Croatia. Additional efforts should be made to prevent cancer-causing behavior such as smoking tobacco. Attention should be directed to an early detection of lung cancer patients, which could provide better treatment options and improve overall survival.

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**Conflict of interest :** None to declare.

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