

# ANALYSIS OF OVERALL SURVIVAL IN PATIENTS WITH LUNG CANCER BEFORE THE INTRODUCTION OF TYROSINE KINASE INHIBITORS AND IMMUNOTHERAPY IN THE REPUBLIC OF CROATIA – A SINGLE INSTITUTION STUDY

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We analyzed outcome in patients with lung cancer (LC) in the period before the introduction of tyrosine kinase inhibitors and immunotherapy in the Republic of Croatia in comparison to similar studies abroad and created a basis for future analysis. At the Pathology Department, Split University Hospital Center, 1165 patients were diagnosed with LC during the 2012-2016 period. Data on age, gender, biopsy specimen, histologic type, and stage of disease were collected. Overall survival of each patient was calculated from the date of biopsy until death or the last day of follow-up. There were 74% of male and 26% of female patients. Median age was 66 years, younger than in other similar studies. In 78% of patients, the diagnosis of LC was based on bronchoscopic biopsy. Adenocarcinoma (ADC) was diagnosed in 42.9%, squamous cell carcinoma (SCC) in 32.7%, and small cell lung carcinoma (SCLC) in 16.7% of cases. In females, ADC was more common than SCC ( $p < 0.001$ ). The mean survival was 22.3 months, median 10 months, and 5-year survival rate was 16.5%. Patients older than 74 years had shorter mean survival compared to younger patients, with the risk of death 1.1 times higher for each increasing age range group ( $p < 0.001$ ). The risk of death was 1.34 times higher in males than females ( $p < 0.001$ ), and 1.12 times higher for SCLC than ADC/SC ( $p = 0.005$ ). Gender, age, and histologic type were confirmed as independent prognostic factors. Women lived on average 8 months longer than men (28 vs. 20.4 months). The 5-year survival rate of 16.5% in the Split-Dalmatia County was better than the one recorded at the national level (10%).

**Key words:** lung cancer, overall survival, personalised therapy, Croatia

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## INTRODUCTION

The incidence of lung cancer (LC) in the Republic of Croatia is high, similar to the rest of the world. In 2015, there were 2998 newly diagnosed patients, 72.3% of males and 27.3% of females (1). Smoking increases the risk of all types of LC. The incidence of LC is higher in urban areas, probably due to air pollution. The incidence of LC is higher in people of lower socioeconomic status and education because they have more frequent smoking habit and are more exposed to other risk factors (2). Discovery of activating mutations (*EGFR*, *ALK*, *ROS1*) in adenocarcinoma (ADC) and tyrosine kinase inhibitors (TKI) led to reflex testing for these mutations in laboratories worldwide (3-5). These analyses have been used in our institution

since 2012, but positive results did not directly affect the treatment, as it was not approved by our national health authorities. Upon discovery of the checkpoint inhibitors, testing for PD-L1 expression in non-small cell lung cancer (NSCLC) was initiated (6). In 2017, we introduced immunohistochemical analysis of PD-L1 into routine diagnostics of NSCLC. Unlike TKI therapy which was introduced several years after testing, immunotherapy (IT) was administered soon after fast approval of health authorities in Croatia (7). In this study, we analyzed overall survival (OS) in LC patients during the 2012-2016 period. The aim was to compare our results with similar studies abroad and create a basis for comparison with the period from 2017 onwards, when targeted TKI and IT became a new paradigm of individualized therapy.

## PATIENTS AND METHODS

The study included 1165 LC patients who were subsequently diagnosed from January 1, 2012, till December 31, 2016 at the Department of Pathology, Forensic Medicine and Cytology, Split University Hospital Center (below, Department of Pathology). Patient data included age, gender, date and type of biopsy, and histopathologic diagnosis. Patients who had small biopsy followed by operative material analysis were included in the cohort only once. For 565 patients, the initial stage of disease was successfully recorded in hospital documentation. Follow-up was completed on December 1, 2017. Patient status (alive or dead) was determined from database of the coroner's office of the Split University Hospital Center and Vital Statistics Registry of the Split-Dalmatia County. Overall survival was calculated in months from the date of biopsy to the day of death or the last day of follow-up. Crude incidence rates of LC in the Split-Dalmatia County were calculated using the 2011 census of the Central Bureau of Statistics of Croatia. Age-standardized incidence rates were calculated with the help of the standard world and European population according to the World Health Organization 2000 (8). The SPSS Statistics for Windows® software package (version 22.0, IBM, Armonk, NY, USA) and Microsoft Excel for Windows (Microsoft Corporation) were used on data processing. The  $\chi^2$ -test, Kruskal-Wallis test, Kaplan-Meier curve, log-rank test, and Cox regression analysis were used on data processing. Results were interpreted at a significance level of  $p < 0.05$ .

## RESULTS

The study included 1165 patients with LC diagnosed at the Department of Pathology from 2012 to 2016. Median age was 66 (min-max: 27-95) years. There were

860 (74%) male and 305 (26%) female patients (Table 1). Patient distribution did not differ significantly in various age range groups ( $\chi^2=3.0$ ;  $p=0.386$ ).

Table 1. Analyzed variables according to gender of patients with lung cancer

		Total	Gender		p*
			Male (N=860)	Female (N=305)	
Age (years) n (%)	≤60	319 (27.6)	224 (26.3)	95 (31.1)	0.386
	>60 to ≤66	289 (25)	218 (25.6)	71 (23.3)	
	>66 to ≤74	296 (25.6)	224 (26.3)	72 (23.6)	
	>74	253 (21.9)	186 (21.8)	67 (22)	
Histologic type n (%)	ADC	500 (43)	332 (38.6)	168 (55.3)	<0.001
	SC	381 (32.7)	327 (38)	54 (17.8)	
	SCLC	195 (16.8)	142 (16.5)	53 (17.4)	
	NEC	20 (1.7)	10 (1.2)	10 (3.3)	
	Other	57 (4.9)	41 (4.8)	16 (5.3)	
Combined	11 (0.9)	8 (0.9)	3 (1)		
Biopsy specimen n (%)	(trans) bronchial	915 (78.5)	683 (79.4)	232 (76.1)	
	CT-guided TTB	89 (7.6)	60 (7)	29 (9.5)	
	Lobectomy	143 (12.3)	106 (12.3)	37 (12.1)	
	Metastasis	18 (1.5)	11 (1.3)	7 (2.3)	

\* $\chi^2$ -test; TTB = transthoracic biopsy

Patients with ADC were most common, 500 (42.9%). Squamous cell carcinoma (SCC) was diagnosed in 381 (32.7%), small cell lung carcinoma (SCLC) in 195 (16.7%), neuroendocrine carcinoma (NEC) in 20 (1.7%), combined cancer in 11 (0.9%) and other malignant lung tumors in 57 (4.8%) cases. Distribution of LC types differed significantly between the sexes ( $\chi^2=48.8$ ;  $p < 0.001$ ). In women, ADC was more common than SCC. Biopsy material was obtained in 78.5% by bronchoscopy, as transbronchial biopsy, followed by computer tomography (CT)-guided transthoracic biopsy (TTB), lobectomy, or biopsy of metastatic tumor. Patient age was significantly different in various types of LC ( $\chi^2 = 17.2$ ;  $p = 0.004$ ) (Table 2).

Table 2. Distribution of patients according to age and biopsy specimen in different types of lung cancer

	Type of lung cancer						p
	Adeno	Squamous	Small cell	Neuro endocrine	Other	Mixed	
Patients (N)	498	380	191	20	56	11	
Age (years) (min-max)	65 (27-91)	67 (44-86)	65 (36-95)	61 (49-81)	66 (39-82)	70 (60-81)	<0.004*
Age (years)							0.106†
≤60	155 (31.1)	86 (22.6)	53 (27)	10	14 (25)	1	
>60 to ≤66	119 (23.9)	96 (25)	53 (27.7)	5	15 (26.8)	1	
>66 to ≤74	120 (24.1)	105 (27.6)	57 (24.6)	2	16 (28.6)	6	
>74	104 (20.9)	93 (24.5)	38 (19.9)	3	11 (19.6)	3	
Biopsy specimen							
Bronchial	368 (73.6)	306 (80.3)	181 (92.8)	14	38 (66.7)	7	
Transthoracic	47 (9.4)	31 (8.1)	6 (3.1)	2	3 (5.3)	0	
Lobectomy	74 (14.8)	44 (11)	3 (1.5)	3	15 (26.3)	4	
Metastasis	11 (2.2)	0 (0)	5 (2.6)	1	1 (1.8)	0	

† $\chi^2$ -test; \*Kruskal-Wallis test

Median age of NEC patients was 61 (min-max: 49-81) years, i.e., 6 years younger than in SCC ( $Z=2.9$ ;  $p=0.004$ ;  $r=0.14$ ), and 9 years younger than in mixed cancer ( $Z=2.8$ ;  $p=0.005$ ;  $r=0.5$ ). Distribution according to age range was not significantly different among particular LC types ( $\chi^2=22.1$ ;  $p=0.106$ ). In all LC types, bronchial biopsy was the most common diagnostic specimen.

In the Split-Dalmatia County, a slight increase in the overall incidence rates of LC and incidence in both men and women was observed during the study period (Figure 1).

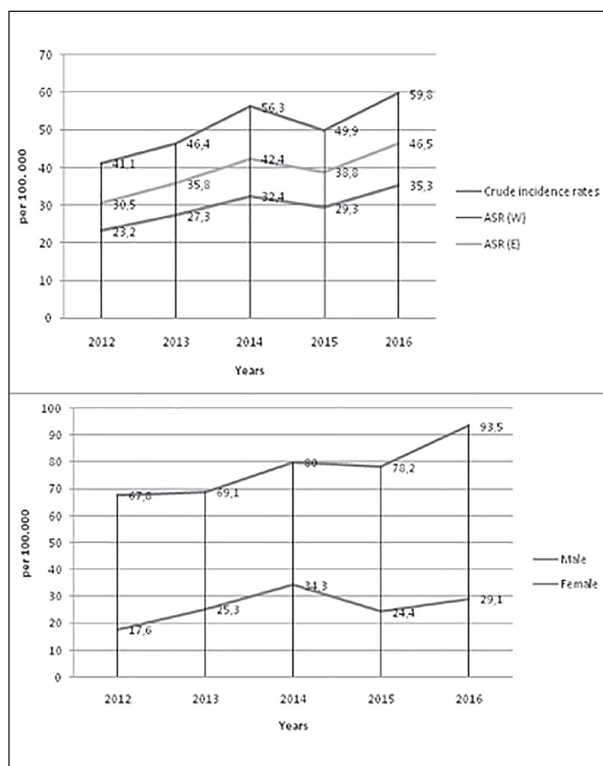


Figure 1. Overview of incidence rates from 2012-2016: total (upper panel) and by gender (lower panel). Crude incidence rates, ASR(W) – age-standardized incidence rates by the standard world population, ASR(E) – age-standardized incidence rates by the standard European population.

Median follow-up was 10 (min-max: 1-69) months. During follow-up, 852 (73%) patients died. All variables were compared with the outcome and the results are shown in Table 3.

Table 3. Comparison of study variables in patients with lung cancer and outcome

		Alive (N=313)	Dead (N=852)	p*
Gender n (%)	male	205 (65)	655 (77)	<0.001
	female	108 (35)	197 (23)	
Age range (years) n (%)	≤60	90 (29.2)	229 (27)	<0.001
	>60 to ≤66	84 (27.3)	205 (24.1)	
	>66 to ≤74	91 (29.5)	205 (24.1)	
	>74	43 (14)	210 (27.4)	
Histologic type n (%)	ADC	141 (45.2)	359 (42.1)	0.278
	SC	107 (34.3)	274 (32.2)	
	SCLC	40 (12.8)	155 (18.2)	
	NEC	4 (1.3)	16 (1.9)	
	Other	18 (5.8)	39 (4.6)	
	Combined	2 (0.6)	9 (1.1)	

\*  $\chi^2$ -test

The share of patients aged >74 years was 1.56 times higher in the group of deceased patients as compared with the alive ones ( $\chi^2=15.87$ ;  $p=0.001$ ). The share of women in the group of alive patients was 1.5 times higher than the share of women in the group of deceased patients ( $\chi^2=14.8$ ;  $p<0.001$ ). Distribution of patients according to LC type did not differ significantly ( $\chi^2=6.3$ ;  $p=0.278$ ).

The mean OS was 22.3 (SE: 0.79; 95% CI: 20.7-23.8) months, median 10 (SE: 0.60; 95% CI: 8.8-11.2) months, and 5-year OS rate was 16.5 (Figure 2). The average survival was by 8 months higher in women than in men (LR: 13.9;  $p<0.001$ ).

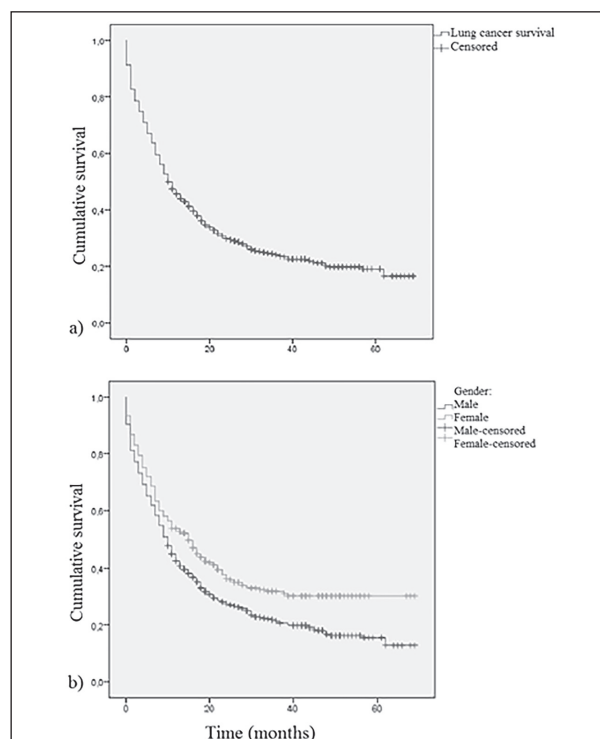


Figure 2. Kaplan-Meier curve of survival of patients with lung cancer: total (upper panel) and by gender (lower panel).

The variables analyzed were compared to OS (Table 4). The groups of patients according to age range had significant difference in OS (LR: 20.9;  $p < 0.001$ ). There was no significant difference in OS between the  $\leq 60$  years,  $>60$  to  $\leq 66$ s and  $>66$  to  $\leq 74$  age groups (LR: 0.085;  $p = 0.059$ ). In these groups, the mean survival was 23.8 months (SE: 0.93; 95% CI: 22-26) and median 12 months (SE: 0.85; 95% CI: 10-14), i.e., significantly higher than in group  $>74$  years (LR: 20.9;  $p < 0.001$ ). A significant difference in OS was found between LC types (LR: 9.1;  $p = 0.028$ ). There was no difference between ADC and SCC (LR: 0.140;  $p = 0.708$ ), and between SCLC and NEC (LR: 0.052;  $p = 0.820$ ). The mean survival in ADC/SC was 22.9 months (SE: 0.92; 95% CI: 21-25), median 12 months (SE: 0.95; 95% CI: 10-14). The mean survival in SCLC/NEC was 18.4 months (SE: 1.7; 95% CI: 15-21.7), median 8 months (SE: 0.7; 95% CI: 6.6-9.3). The median in SCLC/NEC was by 4 months lower than in ADC/SCC (LR: 8.9;  $p = 0.003$ ) (Figure 3).

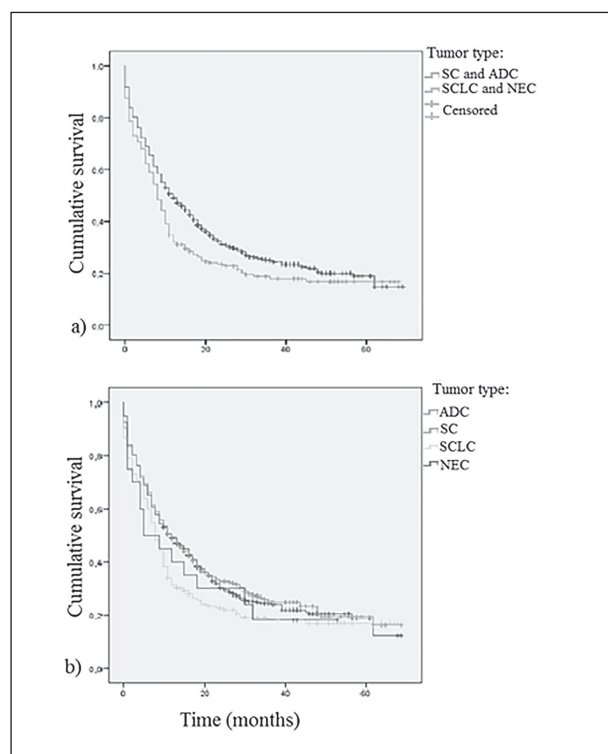


Figure 3. Kaplan-Meier curve of survival of patients with lung cancer according to histologic type.

Patients diagnosed in stage IV of disease had a significantly worse OS (LR: 110.574;  $p < 0.001$ ). Patients diagnosed in stage I to stage IIIC had mean survival of 23.03 months (SE: 1.025; 95% CI: 21-25), median 18 months (SE: 1.729; 95% CI: 14.6-21.4). Patients diagnosed in stage IV had mean survival of 9.26 months (SE: 0.788; 95% CI: 7.7-10.8), median 5 months (SE: 0.569; 95% CI: 3.9-6.1) (Figure 4).

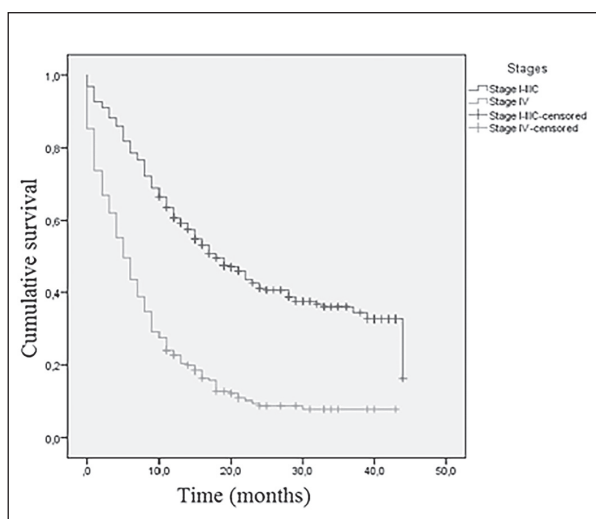


Figure 4. Kaplan-Meier curve of patients with lung cancer according to stage of disease.

The risk of death was 1.34 times higher for men than women ( $p < 0.001$ ). As the age range group was higher, the risk of death increased by 1.13 times compared to the previous age group ( $p < 0.001$ ). The risk of death was 1.12 times higher in patients with SCLC/NEC than with ADC/SC ( $p = 0.001$ ).

Table 4. Study variables according to overall survival

	Survival		p*	HR; 95% CI	p†
	Mean (SE); 95% CI	Median (SE); 95% CI			
Gender					
Male	20.4 (0.9) 18.7-22	10 (0.6) 9-11	<0.001	1.34 1.14-1.57	<0.001
Female <sup>1</sup>	28 (1.7) 25-31	15 (1.8) 11-19			
Age group (years)					
$\leq 60$	24 (1.6) 21-27	11 (1.3) 8.5-13.5	<0.001	1.1 1.07-1.2	<0.001
$>60 \leq 66$	23.5 (1.6) 20-27	13 (1.6) 9.9-16			
$>66 \leq 74$	23.4 (1.7) 20-27	11 (1) 8.9-13			
$>74$	16 (1.4) 13-19	7 (0.9) 5.2-8.8			
Histologic type					
AC	22.5 (1.2) 20-25	12 (1.2) 9.6-14	0.028	1.12 1.04-1.21	<0.005**
SCC	23.4 (1.4) 20.6-26	12 (1.3) 9.5-14.5			
SCLC	18 (1.8) 14.8-22	8 (0.7) 6.7-9.3			
NEC	17.2 (4.3) 8.6-25.7	5 (4) 1-12			

\*Log rank test; †Cox regression; <sup>1</sup>reference level

\*\*Cox analysis investigated the risk of death in SCLC and NEC compared to AC and SCC together. According to LR test, there was no statistically significant difference in survival length between AC and SCC, or between SCLC and NEC.



The risk of death did not differ significantly between SCC and ADC ( $p=0.715$ ). The risk of death was 1.13 times higher in patients with SCLC than ADC (95% CI: 1.03-1.24;  $p=0.01$ ). The risk of death did not differ significantly between NEC and ADC ( $p=0.534$ ). The risk of death did not differ significantly between SCLC and NEC ( $p=0.827$ ). The risk of death for SCLC was 1.3 times higher than for SCC (95% CI: 1.07-1.6;  $p=0.008$ ). The risk of death did not differ significantly between SCC and NEC ( $p=0.452$ ). The risk of death was 1.13 times higher in patients with SCLC than in those with ADC, SCC and NEC combined (95% CI: 1.04-1.24;  $p=0.005$ ). Results of the Cox multivariate regression analysis suggested that patient gender, age, and histologic type were statistically significant parameters for outcome (Table 5).

Table 5. Results of multivariate Cox regression analysis in patients with lung cancer

	HR; 95% CI	p*
Gender Male Female <sup>†</sup>	1.34 (1.14-1.59)	<0.001
Age (years) ≤60 >60 to ≤66 >66 to ≤74 >74	1.13 (1.06-1.2)	<0.001
Histologic type AC SCC SCLC NEC	1.4 (1.2-1.7)	<0.001**

<sup>†</sup>Reference level; \*Cox regression

\*\*Cox analysis investigated the risk of death in SCLC and NEC compared to AC and SCC together. According to LR test, there was no statistically significant difference in survival length between AC and SCC, or between SCLC and NEC.

## DISCUSSION

Lung cancer is the most common and lethal malignancy in the world, thus an important health problem. It is mostly caused by tobacco use, so reducing the prevalence of smoking worldwide has priority in fighting the disease. Most patients are diagnosed at an advanced stage of the disease (9); in our cohort, 80.1% of patients were in stage III or IV. Early LC stages have a more favorable prognosis, with 5-year survival rates of 70%-90% for small, localized tumors (10-12). Earlier diagnosis should be a priority. The large American National Lung Screening Trial from 2011 showed that screening with low-dose CT reduced LC mortality (13). The study showed that after positive screening results, LC stages Ia and Ib were diagnosed most frequently. In Croatia, the screening program for early

detection of LC with low-dose CT started in 2020, and we are hoping to see lower percentage of patients diagnosed in advanced stages (14).

In the Split-Dalmatia County, LC occurs at a younger age than in the rest of the world; in our cohort, median age was 66 years, compared to median age of 70 in the USA (15). We also observed a higher ratio of men to women affected with LC than in the rest of the world (male: female 2.8:2.13) (16). In the world, there is a downward trend in the incidence of LC in men and an increased incidence in women (17). According to the model reported by Lopez *et al.*, it takes 40 years for changes in smoking rates (prevalence) to affect epidemiological LC statistics (18). Today, developed countries have a declining trend of LC incidence in men owing to decreased tobacco use in the last several decades. Since the smoking epidemic in women started later, a decreasing incidence is not yet observed. According to Janković *et al.*, Croatia followed the world trend of a decreasing incidence of LC in men and increasing incidence in women from 1988 to 2013 (19,20). However, our study showed a slight increase in the incidence in both genders in the Split-Dalmatia County from 2012 to 2016. The incidence of LC in 2012 worldwide (age-standardized rates according to the standard world population) was 23.1/100 000, 30.4/100 000 in Croatia, and 23.2/100 000 in the Split-Dalmatia County (16).

The most common type of primary LC in our cohort was ADC (43%), and its proportion was increased in the monitored period. This result is in line with the world literature where ADC is the most common type, with a trend of increasing incidence, followed by SCC (21). In men, the proportion of ADC is slightly higher than SCC (38.6% vs. 38%), while in women the difference was significant (55.3% vs. 17.8%). These results correspond to the results of other world studies according to which a decreased incidence of SCC in men has been observed in recent decades in favor of ADC. The changes in the incidence are attributed to a decrease in the smoking rate and change in the quality of cigarette filters (22). The incidence of ADC in women is higher than SCC worldwide, which was confirmed by this study (21). The incidence of SCLC was 16.7%, which corresponds to data from the world literature (23). A few neuroendocrine carcinomas were diagnosed at a younger age, median age 61 (min-max: 49-81) years, which is consistent with literature data. According to the studies by Travis *et al.*, most atypical carcinoids occur between 45 and 55 years (23), and patients with large cell NEC have a median age of 60 years at the time of diagnosis (24). LC is the leading cause of death from all malignancies (16). In most countries, the 5-year survival rate of patients with LC is 10%-20%, and in Croatia it is 10% (25). In our cohort, the mean survival was 22.3 months, median

10 months, and the 5-year survival rate is 16.5%. In the 2010-2014 period, the best 5-year survival of patients with LC was recorded in Japan (32.9%) (25). The following 12 countries had a 5-year survival rate of 20%-30%: USA, Canada, Mauritius, China, Korea, Taiwan, Israel, and in Europe Latvia, Iceland, Sweden, Switzerland and Austria. Countries that had a 5-year survival rate of less than 10% were India, Thailand and Bulgaria (25). According to these data, 5-year survival of LC in the Split-Dalmatia County was 16.5% *versus* 10% at the national level. The literature shows that female gender is a favorable prognostic factor for OS. A meta-analysis by Nakamura *et al.* including 86 800 patients with NSCLC found a significantly longer survival in women (26). In several studies on SCLC, female gender had a favorable prognostic significance (27-29). In our study, women had 8 months longer mean survival than men (LR: 13.9;  $p < 0.001$ ), which is in line with data from the world literature. Also, the proportion of women was 1.5 times higher in the group of alive patients than in the deceased ones ( $p < 0.001$ ), and the number of men was higher in the deceased group. In a large Norwegian study involving 40 118 patients with all types of LC, the risk of death was 1.14 times higher for men than for women (95% CI: 1.109-1.166;  $p < 0.001$ ) (30). In our study, these results were confirmed, with the risk of death for men 1.34 times higher than for women (95% CI: 1.14-1.57,  $p < 0.001$ ). According to data from the world literature, older patients with LC have a worse prognosis than younger patients (31-33). In our study, patients older than 74 had a significantly worse survival than patients aged  $\leq 74$  ( $p < 0.001$ ). Also, in the group of deceased, there was a significantly higher number of patients older than 74 than in the group of alive patients (27.4% *vs.* 14%) ( $p = 0.001$ ). There was no difference between ADC and SCC in median survival, which was 12 months ( $p = 0.708$ ), and this result is consistent with the literature (30,33). Patients with SCLC had lower median survival, 8 months (95% CI: 6.7-9.3), which correlates with data from the literature (15,30).

## CONCLUSION

During the 2012-2016 period, the incidence of LC in the Split-Dalmatia County was slightly increased in both sexes, and patient age of 66 years was somewhat younger than in similar studies. Gender, age, and type of cancer were independent prognostic factors, confirming the results of other clinical and population studies. The 5-year survival rate of 16.5% was higher than at the national level. A limitation of this study was its epidemiologic descriptive character, while its strength were real clinical data from one center with a large catchment population. This study may provide a basis for future analyses with new personalized therapies.

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## SAŽETAK

### ANALIZA OPĆEG PREŽIVLJENJA BOLESNIKA S KARCINOMOM PLUĆA PRIJE UVOĐENJA INHIBITORA TIROZIN KINAZE I IMUNOTERAPIJE U REPUBLICI HRVATSKOJ – STUDIJA IZ JEDNE USTANOVE

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Analizirali smo ishod ispitanika s karcinomom pluća u razdoblju prije uvođenja inhibitora tirozin kinaze i imunoterapije u Republici Hrvatskoj, rezultate usporedili sa sličnim studijama i stvorili osnovu za buduće analize. Na Odjelu za patologiju KBC-a Split od 2012. do 2016. godine karcinom pluća je dijagnosticiran u 1165 bolesnika. Prikupljeni su podatci o dobi, spolu, bioptičkom uzorku, histološkom tipu karcinoma i stadiju bolesti. Ukupno preživljenje za svakog bolesnika izračunato je od datuma biopsije do datuma smrti, odnosno posljednjeg dana praćenja. Sedamdesetčetiri posto ispitanika bili su muškarci, a 26 % žene, medijan dobi 66 godina (manji nego u sličnim studijama). U 78 % slučajeva dijagnoza je postavljena bronhoskopskom biopsijom. Adenokarcinom (ADC) je dijagnosticiran u 42,9 %, skvamozni karcinom (SCC) u 32,7 % i karcinom malih stanica (SCLC) u 16,7 % slučajeva. U žena je ADC bio češći od SCC ( $p < 0,001$ ). Prosječno preživljenje bilo je 22,3 mjeseca, medijan 10 mjeseci, a stopa petogodišnjeg preživljenja 16,5%. Bolesnici u skupini starijih od 74 godine imali su kraće prosječno preživljavanje u odnosu na mlađe skupine, s rizikom smrti 1,1 puta većim za svaku višu dobnu skupinu ( $p < 0,001$ ). Rizik smrti bio je 1,34 puta veći za muškarce nego za žene ( $p < 0,001$ ), a 1,12 puta veći za SCLC od ADC/SC ( $p = 0,005$ ). Spol, dob i histološki tip karcinoma potvrđeni su kao neovisni prognostički čimbenici. Žene su u prosjeku živjele 8 mjeseci duže od muškaraca, 28 naspram 20,4 mjeseca. Petogodišnja stopa preživljenja od 16,5 % u našoj kohorti bila je bolja nego na nacionalnoj razini, 10 %.

**Ključne riječi:** rak pluća, opće preživljenje, personalizirana terapija, Hrvatska