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EPIDEMIOLOGICAL ANALYSIS OF PROGRESSION-FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS) IN NON-SMALL-CELL LUNG CANCER PATIENTS IN REPUBLIC OF MACEDONIA

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Abstract

Lung cancer represents the leading cause of cancer mortality worldwide, accounting for ~1.2 million deaths each year. Improving survival in lung cancer is a major challenge for modern oncology considering that 5-year survival remains < 15%, across all stages of the disease with < 7% of patients alive 10 years after diagnosis. About 85% to 90% of lung cancers are non-small-cell lung cancer (NSCLC). Lung cancer is the leading cause of cancer-related mortality in Macedonia with more than 900 newly diagnosed lung cancer patients per year. The motive for undertaking the study was precisely the lack of adequate statistical data on treatment outcomes and survival rates of non-smal-cell lung cancer patients in the country. The main goal was to provide an assessment of progression-free survival and overall survival in NSCLC patients treated at UCRO-Skopje, over the past three years: 2009–2011. The research represents a follow-up study. The study was based on filling in forms for an epidemiological analysis of PFS and OS in NSCLC patients. These forms contain demographic, clinical and histological data, as well as dates of diagnosis, treatment initiation and outcomes. Data were collected from patient files for a period of three years (2009–2011), collected through the registration of each NSCLC patient treated in the period of the investigation. The statistical series were analysed by determining the ratio, proportions, chi-square and Student t-test and survival analysis. The study included 1002 patients with NSCLC treated at the UCRO, of whom 859 were males and 137 were females, and 0.6% missing data for gender. The average age of patients was 60.4 ± 9.0 y., min. of 19 y., max. of 85 y. Most of the patients were smokers- 86.9%. The dominant stage in NSCLC was stage IV, with 36.3%, followed by IIIA 17.5%, stages IIIB and IIB with 13.6% and so on. In the examined group of patients the most common subtype was 56.9% with planocellular, 28.2% with adenocarcinoma, large-cell with 7.7% and missing / no closer subtype 7.2%. Median survival from diagnosis to the last check-up/death was 6.2 m. 25% of patients with NSCLC from diagnosis to the last check-up/death died in the first 2.5 m and 25% survived more than 11.1 m. Median survival from treatment outset to the last check-up/death was 5.4 m. 25% of patients with NSCLC survived for two months from the outset of treatment to the last check-up/death and 25% survived for more than 10.8 m. In the course of the study we found that the median survival in 2009, 2010 and 2011 differed from the diagnosis to the last control/death. In 2009, median survival was 7.5 m and we registered a statistically significantly longer survival compared to 2010 – 6.1 m, and 2011 – 5.4 m. Similar data and conclusions were received in calculating the survival from therapy to the last check-up/death. Median survival in 2009 was 6.2 m and this is a statistically significant longer survival compared with 2010 (5.9 m) and 2011 (4.6 m). The results indicate that compared with international data patients with NSCLC had a shorter life of survival.We hope that this study will help to improve the future treatment of non-small-cell lung

cancer patients through optimizing the treatment for every single patient, which will help in longer patient survival. Precise determination of these data provides for a proper selection of the best treatment option and optimized therapy for every patient.

Key words: non-small-cell lung cancer, epidemiology, survival.

Introduction

According to the World Health Organization (WHO), lung cancer is the leading cause of cancer-related deaths in both men and women. There are more than 1.2 million new cases of lung and bronchial cancer each year worldwide, causing approximately 1.1 million deaths annually [1–3]. In Europe, it is estimated that there were approximately 381,500 new cases of lung cancer in 2004, with an average 341,800 deaths, that is 936 deaths every day. Lung cancer is reported to be the single largest cause of cancer deaths in the world, responsible for 18.7 percent of all cancer deaths. An estimated 1.6 million new lung cancer cases are diagnosed worldwide each year. The highest incidence rates in males are observed in Central/Eastern and Southern Europe (57 and 49 per 100,000, respectively), whereas in women the highest rates are found in Northern Europe (36 per 100,000). Five-year survival rates of lung cancer patients have only slightly improved over the past decade and remain low at 10% [4–5].

Lung cancer represents the leading cause of cancer mortality worldwide, accounting for ~1.2 million deaths each year. Improving survival in lung cancer is a major challenge for modern oncology considering that 5-year survival remains < 15%, across all stages of the disease with < 7% of patients alive 10 years after diagnosis. Because of the difficulties in significantly improving survival in locally advanced and metastatic non-small-cell lung cancer (NSCLC), diagnosis and treatment of early stages theoretically represent the most consistent possibility of modifying the outcome of NSCLC in terms of disease-free and overall survival [6].

The survival rate depends on the stage at which the cancer is diagnosed and what treatment option is adopted. The survival time experienced by an individual patient may be much higher or lower, depending on the specific patient and the tumour characteristics. The average survival for a patient with advanced NSCLC after relapse is only four months and only if treated with the best supportive care (BSC). Although various chemotherapeutic agents were developed in the late 1980s and 1990s, platinum doublet therapy seems to reach a therapeutic plateau with an objective response rate of 30–40% and median survival time (MST) of 8–10 months for patients with stage IIIB or IV disease [7].

The development of EGFR-TKIs and the discovery of EGFR gene mutations have provided a great opportunity to develop individuallized therapies for lung cancer. Therefore, today it is possible to individualize treatment of lung cancer by selecting patients according to EGFR mutational status, histological type of lung cancer, age, gender, smoking history and other biomarkers. Many retrospective analyses suggest that certain subsets of patients may derive a greater benefit than others, e.g. patients with adenocarcinoma histology, Asian origin, female gender, or absence of smoking history have a greater benefit with EGFR-TKIs. However, the clinical benefit seen with TKIs is not limited only to patients with these clinical characteristics. Deselecting patients from certain subgroups means that some patients who may derive benefit would be excluded from treatment [8–17].

Lung cancer is the leading cause of cancer-related mortality in Macedonia with more than 900 newly diagnosed lung cancer patients per year [18]. The high mortality is mainly because the majority of NSCLC cases are diagnosed at an advanced stage, then the early development of systemic disease, resistance to currently available treatment strategies and unavailable novel treatment options for NSCLC [19].

It would be possible to individualize treatment of lung cancer in the Republic of Macedonia, by selecting patients according to EGFR mutational status, other biomarkers and clinical characteristics. Personalized therapy based on clinical, histological and molecular factors will improve patient outcomes. Because

of all this, there is a need for verification and in-depth analysis of epidemiological characterristics and clinical outcomes of non-small–cell lung cancer patients, a need that is rapidly growing and becomes an important factor in treatment selection and treatment outcomes [19].

Motive

The motive for undertaking the study was precisely the lack of adequate statistical data on treatment outcomes and survival rates of non-small-cell lung cancer patients in the country. We hope that the study will provide data for the epidemiological and histological characteristics of lung cancer in Macedonia, and clinical outcomes of lung cancer patients treated in Macedonia, which data will be very useful in the future planning and organization of health care, improving diagnosis, histological assessment of disease and selection of the most appropriate treatment option for each patient suffering from non-small-cell lung cancer.

Goals

The main goal was to provide assessment of progression-free survival (PFS) and overall survival (OS) in non-small-cell lung cancer patients, treated at the University Radiotherapy and Oncology Clinic (UCRO), Skopje, for the period of the past three years: 2009–2011.

Our mission was to understand and analyse the specific characteristics of lung cancer, particularly non-small-cell lung cancer (NSCLC), and their correlation with progression-free survival (PFS) and overall survival (OS) in non-small-cell lung cancer patients in Macedonia, and help to improve the future treatment of non-small-cell lung cancer patients through optimizing the treatment for every single patient.

Precise determination of these data provides a proper selection of the best treatment option and optimized therapy for every patient.

Material and methods

The research represents a follow-up study, which was developed at the UCRO Skopje. The study is based on filling in forms for the epidemiological analysis of PFS and OS in non-small-cell lung cancer patients in Macedonia. These forms contain demographic data (patient age at the time of diagnosis, gender, smoking status), clinical and histological data (NSCLC staging-TNM classification, subtype of NSCLC), as well as dates of diagnosis, treatment initiation and outcomes. Data were collected from patient files for a period of three years (2009–2011), collected through the registration of each NSCLC patient treated in the period of the investigation. The study was conducted by doctors – specialists in radiotherapy and oncology – filling in the data for non-small-cell lung cancer (NSCLC) patients treated at UCRO Skopje in the past 3 years in the forms for epidemiological analysis of PFS and OS of NSCLC patients in Macedonia.

The statistical series were analysed by determining the ratio of relations, proportions and ratios. Statistical significance between the detected differences was determined by the chis-quare test and Student t-test. We used Survival Analysis: Kaplan & Meier curve, comparing two samples, comparing multiple samples and Proportion Hazard (Cox) regression. The results are shown in graphs and in tables.

Results

The study included 1002 patients with NSCLC treated at the Radiotherapy and Oncology Clinic, Skopje, of whom 859 (85.7%) were males and 137 (13.7%) were females, and 0.6% missing data for gender (Table 1). The percentage difference registered between the sexes was statistically significant for $p = 0.00000$.

The average age of patients was 60.4 ± 9.0, minimum 19, maximum 85, median 60 and 58 mode. The average age of male patients was 60.8 ± 8.9 y., minimum 19, maximum 85, median 61. The average age of the female patients was 57.5 ± 8.8, minimum 33, maximum 74, median 58. The percentage difference between the genders registered (the Mann-Whitney U test) was statistically significant for $p = 0.000234$ (Table1).

Table 1

Distribution of gender, age, smoking, stage, subtype, average time from diagnosis-treatment and diagnosis-last check-up

Sex				**n (%)**			
Men				859 (85.7)			
Women				137 (13.7)			
Missing				6 (0.6)			
Average of age	60.4 y	minimum 19 y		maximum 85 y		± St.Dev. 9.0	
Men	60.8 y	minimum 19 y		maximum 85 y		± St.Dev. 8.9	
Woman	57.5 y	minimum 33 y		maximum 74 y		± St.Dev. 8.8	
Smoking	**yes** n (%)		**no** n (%)		**missing** n (%)		
total	871 (86.9)		51 (5.1)		80 (8.0)		
Men	790 (92.0)		13 (1.5)		56 (6.5)		
Women	80 (58.4)		38 (27.7)		19 (13.9)		
Stage NSCLC				**n (%)**			
IA				12 (1.2)			
I B				72 (7.2)			
IIA				54 (5.4)			
IIB				136 (13.6)			
IIIA				175 (17.5)			
IIIB				136 (13.6)			
IV				364 (36.3)			
Missing				53 (5.3)			
Subtype NSCLC				**n (%)**			
planocelullar				570 (56.9)			
adenocarcinoma				283 (28.2)			
Large cell				77 (7.7)			
missing/no closer subtype				72 (7.2)			
Average time diagnosis-treatment							
1.3 m	minimum 0.03 m		maximum 31.5 m		± St.Dev. 2.3		
Average time diagnosis-last check up/death							
8.5 m	minimum 0.0 m		maximum 62.9 m		± St.Dev. 8.9		
Patients who reached				**n (%)**			
Therapy				995 (99.3)			
I progression				357 (35.6)			
II progression				87 (8.7)			

Most of the patients in the group, 86.9%, were smokers – 92.0% of male were smokers and 58.4% of the women smoked. The percentage difference registered between the genders in terms of smoking was statistically significant for p = 0.0000 (Table 1). NSCLC were registered in patients who did not smoke – 5.1% of the total group, 1.5% of males and 27.7% of females.

The dominant stage in NSCLC was stage IV, 36.3%, followed by IIIA, 17.5%, stages IIIB and IIB, 13.6%, stage IIA, 5.4%, IA – 1.2% and IB – 7.2% (Table 1)

In the examined group of patients the most common subtype was planocelullar, 56.9%, then 28.2% with adenocarcinoma, 7.7%, with large cell and 7.2% missing/no closer subtype The percentage difference registered between planocelullar subtype versus other modes of subtypes was statistically significant for p = 0.0000 (Table 1). The most common subtype was planocelullar subtype, represented in 60.0% in the males patients, but in the female patients the most common subtype was adenocarcinoma – 46.0%.

In 5.9% (59) of the total number of patients the date of diagnosis or date of treatment was missing. In 180 (18.0%) of the patients the date of diagnosis and treatment were the same, and for that reason it was not possible to determine their average time from diagnosis and treatment initiation to the last check-up/death.

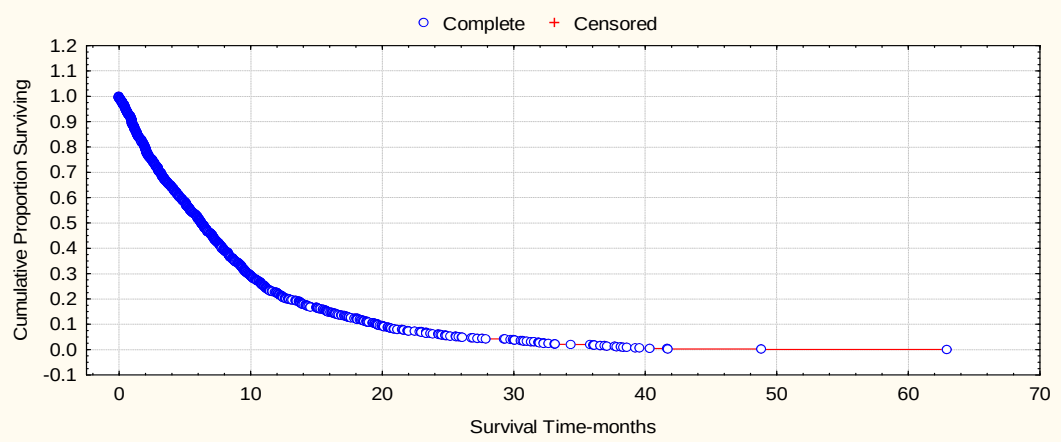
The average time from diagnosis to therapy in the test period was 1.3 ± 2.3 m, with a median of 0.6, minimum 0.03 and maximum of 31.5 m. (Table 1)

In 5.0% of the total number of patients the data of diagnosis and in 0.6% that of the date of last check-up were missing; they were excluded from further analysis. 0.7% of patients had the same date of diagnosis, date of treatment starting and date of final check-up/death.

The average time from diagnosis to the last check up/death in the test period was 8.5 ± 8.9 m, minimum 0.0 and maximum 62.9 m. (Table 1) The average time from diagnosis to the last check-up/death in 2009, was 11.4 ± 11.2 m, with a median of 7.5 m., minimum of 0.0 and maximum of 62.9 m. The average time from diagnosis to the last check-up/death in 2010 was 8.1 ± 7.2 m, with a median of 6.1 m., minimum of 0.0 and maximum of 32.7 m. The average time from diagnosis to the last check up/death in 2011 was 6.3 ± 4.9 m, with a median 5.4 m., minimum 0.0 and maximum of 35.8 m. According to the Analysis of Variance test, the difference between the average time in the investigation period – years from diagnosis to the last check-up/death – is statistically significant – F = 3270769, p = 0.000000. The Tukey HSD test, that gives an individual difference in the average time from diagnosis to the last control, is statistically significant between 2009 versus 2010 and 2011 (p = 0.000023 and p = 0.000022).

Median survival is the amount of time at which 50% of people with a condition will have died, and 50% are still alive. Median survival from diagnosis to the last check-up/death was 6.2 m.

25% of patients with NSCLC from diagnosis to the last check-up/death died in the first 2.5 m. and 25% survived for more than 11.1 m. (Graph 1).

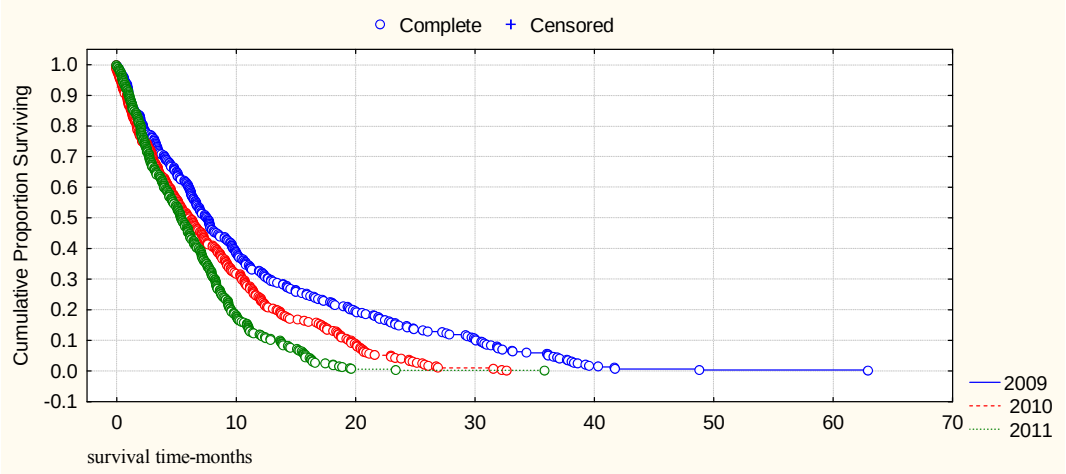


Graph. 1 – Kaplan-Meier curve of overall survival from diagnosis to last check-up/death

25% of patients with NSCLC in 2009 died in the first 3.2 m. from diagnosis to the last check-up/death. 50% of all patients survived 7.5 m., and 25% survived for more than 15.9 m. 25% of patients with NSCLC in 2010 died in the first 2.1 m. from diagnosis to the last check-up/death. 50% of all patients survived for 6.1 m., and 25% survived for more than 11.5 m. 25% of patients with NSCLC in 2011 y., die first 2.3 m., from diagnosis to the last check-up/death. 50% of all patients survived for 5.4 m., and 25% survived for more than 8.8 m. (Graph 2). We registered a statistically significant association between survival and year of diagnosis (Chi-square = 24.80371, p = 0.0000).

During the research no significant statistical difference was registered in survival between the two sexes and survival between smokers and non-smokers for p > 0.05 (Long-Rank test). And we did not register any statistically significant association between survival and the subtype of NSCLC from diagnosis to the last check-up/death (Chi-square = 3.873038, p = 0.14427). Nor did we register any statistically significant association between survival and the age of the patients from diagnosis to the last check-up/death (Chi-square = 8.376454, p = 0.07875).

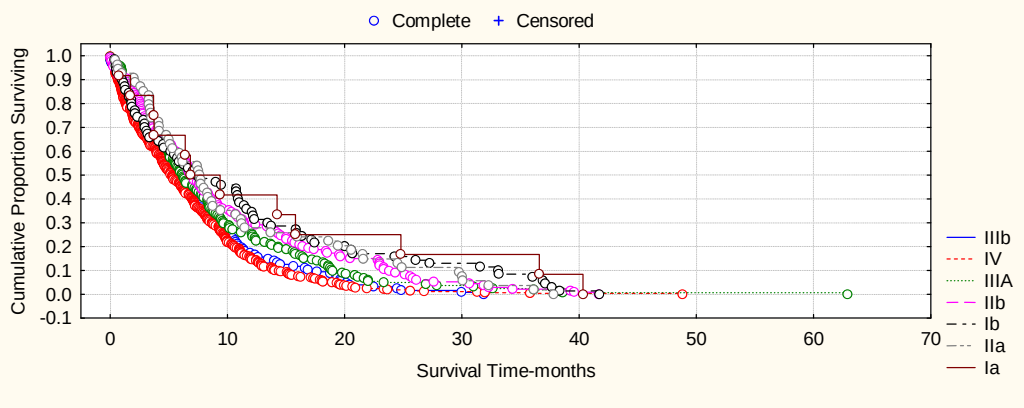
25% of patients with stage IV NSCLC died in the first 1.9 m. from diagnosis to the



Graph. 2 – Kaplan-Meier curve of overall survival from diagnosis to last check-up/death by year of diagnosis

last check-up/death. 50% of all patients survived for 5.2 m., and 25% survived for more than 9.7 m. (Graph 3).

25% of patients with stage IIIA NSCLC died in the first 2.4 m. from diagnosis to the last check-up/death. 50% of all patients survived for 6.2 m., and 25% survived for more than 12.3 m. 25% of patients with stage IIIB NSCLC died in the first 2.9 m. from diagnosis to the last check-up/death. 50% of all patients survived 6.5 m., and 25% survived for more than 10.1 m. (Graph 3).



Graph. 3 – Kaplan-Meier curve of overall survival from diagnosis to last check-up/death by stage

25% of patients with NSCLC stage IIA died in the first 3.5 m. from diagnosis to the last check-up/death. 50% of all patients survived for 7.6 m., and 25% survived for more than 14.8 m. 25% of patients with NSCLC stage IIB died in the first 2.9 m from diagnosis to the last check-up/death. 50% of all patients survived for 7.1 m., and 25% survived for more than 14.4 m. (Graph 3).

25% of patients with stage IA NSCLC died in the first 3.7 m. from diagnosis to the last check-up/death. 50% of all patients survived for 6.8 m., and 25% survived for more than 15.8 m. 25% of patients with stage IB NSCLC died in the first 2.2 m. from diagnosis to the last check-up/death. 50% of all patients survived for 7.3 m., and 25% survived for more than 16.1 m. (Graph 3). We registered a statistically significant association between survival and stage of NSCLC from diagnosis to the last check-up/death (Chi-square = 223.33827, p = 0.00105).

Using Proportional Hazard (Cox) regression variables, gender, age, stage and subtype, significantly correlate with survival in NSCLC by setting diagnosis to the last check-up/death (Chi-square = 37.7943, p = 0 .00000), based on the Wald statistics for each variable, age and stage were significant predictors of survival of the same (p = 0.045813 and p = 0.000000) (Table 2).

Table 2

Proportional hazard (Cox) regression

N = 1002	Beta	Standard error	t-value	Exponent beta	Wald statistic	p
age	0.073102	0.036602	1.99719	1.075840	3.98879	0.045813
gender	-0.117325	0.104158	-1.12641	0.889296	1.26880	0.260001
smoking	-0.289238	0.164440	-1.75893	0.748834	3.09383	0.078599
stage	-0.082800	0.015726	-5.26513	0.920535	27.72156	0.000000
subtype	-0.016404	0.052158	-0.31451	0.983730	0.09891	0.753138

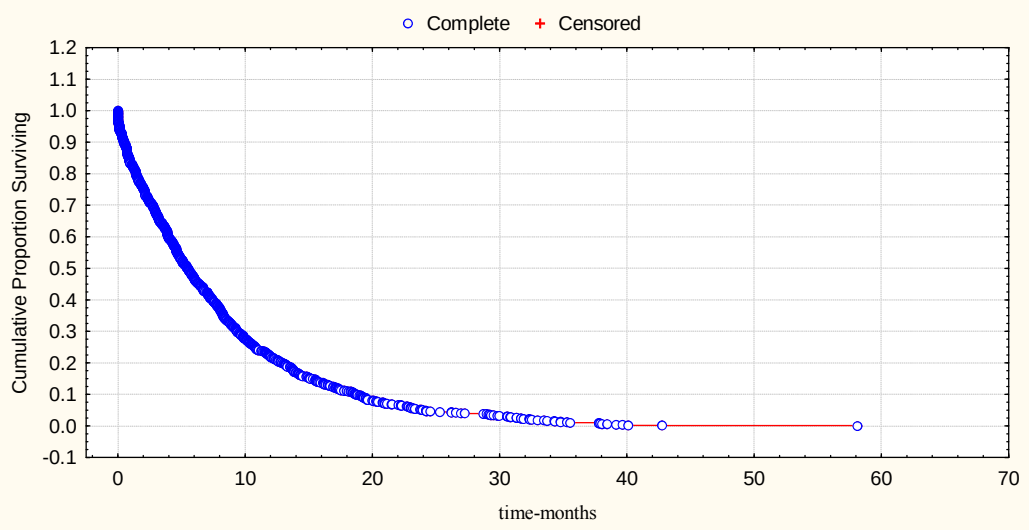
In the investigated period, in 2009–11, 99.3% of all patients received treatment, 0.7% of patients died the same day that they were placed on therapy, 35.6% of all patients achieved I progression, 8.7% of all patients reached II progression (Table 1).

Median survival from diagnosis to I progression was 7.6 m and from diagnosis to II progression was 15.6 m.

Median survival from treatment outset to I progression was 6.2 m and from treatment outset to II progression it was 14 m.

Median survival from treatment outset to the last check-up/death was 5.4 m.

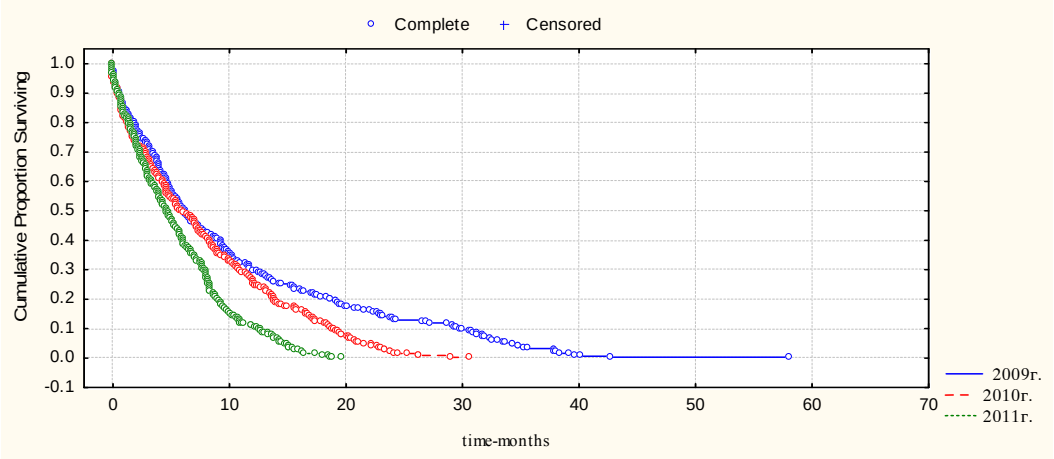
25% of patients with NSCLC survived for two months from the outset of treatment to the last check-up/death and 25% survived for more than 10.8 m. (Graph 4).



Grapf. 4 – Kaplan-Meier curve of overall survival from treatment to last check-up/death

During the research no significant statistical difference in survival between the two genders and survival between smokers and non-smokers was registered for $p > 0.05$ (Long-Rank test.

In 2009, 25% of the patients with NSCLC died in the first 2.4 m. from the outset of treatment to the last check-up/death, 50% of all patients survived 6.2 m., and 25% survived for more than 14.9 m. In 2010, 25% of the patients with NSCLC died in the first 1.7 m. from the outset of treatment to the last check-up/death, 50% of all patients survived for 5.9 m., and 25% survived for more than 12.3 m. In 2011, 25% of patients with NSCLC died in the first 1.9 m. from the outset of treatment to the last check-up/death, 50% of all patients survived for 4.6 m., and 25% survived for more than 8.3 m. (Graph 5). We registered a statistically significant association between survival and year of diagnosis (Chi-square = 23.00441, $p = 0.00001$).



Graph. 5 – Kaplan-Meier curve of overall survival from treatment to last check-up/death by year of diagnosis

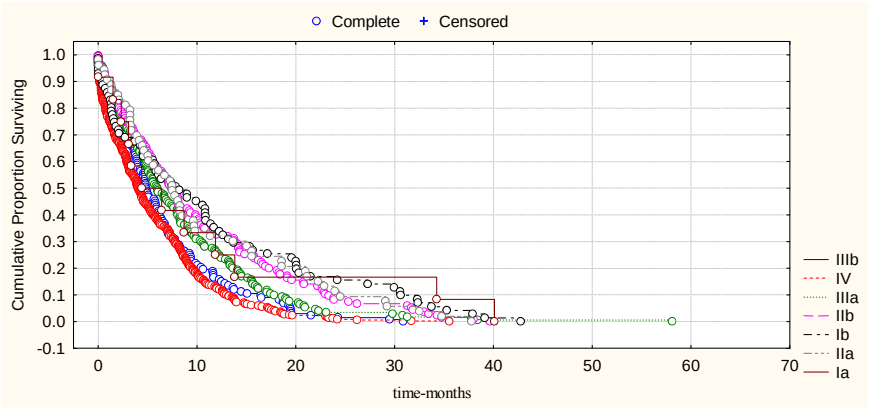
During the research a significant statistical association in survival between the ages of the patients was registered (Chi-square = 11.43058, p = 0.02214).

25% of patients with stage IV NSCLC died in the first 1.2 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 4.1 m., and 25% survived for more than 9.6 m. (Graph 6).

25% of patients with stage IIIA NSCLC died in the first 2.4 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 6.0 m., and 25% survived for more than 12.2 m. 25% of patients with stage IIIB NSCLC died in the first 2.1 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 4.8 m., and 25% survived for more than 9.3 m. (Graph 6).

25% of patients with NSCLC stage IIA died in the first 3.3 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 7.5 m., and 25% survived for more than 15.5 m. 25% of patients with NSCLC stage IIB died in the first 3.0 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 7.4 m., and 25% survived for more than 15.1 m. (Graph 6).

25% of patients with stage IA NSCLC died in the first 2.3 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 7.4 m., and 25% survived for more than 11.9 m. 25% of patients with stage IB NSCLC died in the first 1.6 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 8.3 m., and 25% survived for more than 11.9 m. (Graph 6).

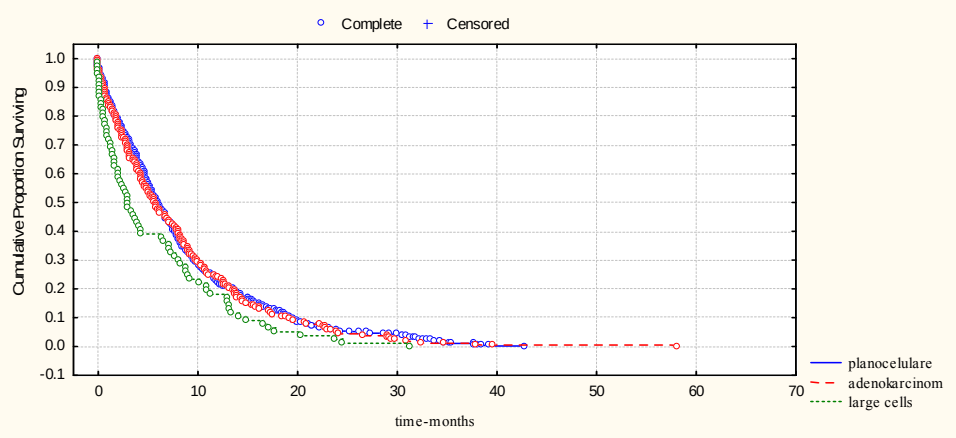


Graph. 6 – Kaplan-Meier curve of overall survival from treatment to last check-up/death by stage

We registered a statistically significant association between survival and stage of NSCLC from the outset of treatment to the last check-up/death (Chi-square = 46.2740, p = 0.00000).

We registered a statistically significant association between survival and subtype of NSCLC from the outset of treatment to the last check-up/death (Chi-square = 9.524417, p = 0.00855).

25% of patients with subtype planocelullar NSCLC died in the first 2.4 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 6.0 m., and 25% survived for more than 11.4 m. 25% of patients with subtype adenocarcinoma NSCLC died in the first 2.2 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 5.7 m., and 25% survived for more than 11.0 m. 25% of patients with subtype large cells NSCLC died in the first 0.7 m. from the outset of treatment to the last check-up/death. 50% of all patients survived for 3.0 m., and 25% survived for more than 9 m. (Graph 7).



Graph. 7 – Kaplan-Meier curve of overall survival from treatment to last check-up/death by subtype

Discussion

With its high incidence and mortality, cancer is a challenge to modern epidemiology and clinical medicine. Each year around 10.9 million newly–registered cases are diagnosed worldwide. More than 6.7 million patients die from cancer [20].

Lung cancer is the most common in the world, but with large differences between individual areas. It is dominant among men in many countries, although there are exceptions, such as Portugal and Japan or India, where the dominance is gastric and oral cavity cancer. About 85% to 90% of lung cancers are non-small-cell lung cancer (NSCLC). There are 3 main subtypes of NSCLC. The cells in these subtypes differ in size, shape, and chemical make-up when looked at under a microscope. But they are grouped together because the approach to treatment and prognosis (outlook) are often very similar. Survival in patients with lung cancer is negative – only 10% survive for five years [19].

Non-small-cell lung cancer accounts for at least 80% of lung cancers in the United States. It does not spread as rapidly as small-cell lung cancer, but is still frequently diagnosed after a surgical cure is not possible. Smoking is the leading cause of lung cancer, but factors other than smoking are more likely to contribute to this type of lung cancer. There are 3 primary types of non-small-cell lung cancer. Adenocarcinoma is the most common form of non-small-cell lung cancer, accounting for up to 50% of cases in the United States. It is usually the type of lung cancer found in non-smokers, and is the most common type seen in women [21]. In our study the most recorded subtype was planocelullar in men, 60%, and adenocarcinoma in women, 46%.

Survival was highest in patients with adenocarcinoma (1-year survival: 29.1%) and lowest in those with large cell tumours (1-year survival: 12.8%) [22].

In our investigation period we registered a statistically significant association between survival and subtype of NSCLC from the outset of treatment to the last check-up/death. 50% of patients with subtype planocelullar NSCLC survived for 6.0 m. and 50% of patients with sub-

type adenocarcinoma survived for 5.7 m from the outset of treatment to the last check-up/death. 50% of patients with subtype large cell NSCLC survived for 3.0 m from the outset of treatment to the last check-up/death.

The latest survival rates for lung cancer in England for 2005–09 show that 29.4% of men are expected to survive their disease for at least one year, falling to 7.8% surviving five years or more [23–24]. Our study shows that for 2009–2011 25% of the men were expected to survive their disease for at least 11 months.

The survival rates for women are similar, with 33% expected to survive for one year or more and 9.3% surviving for at least five years. Broadly similar rates have been reported for Wales, Scotland and Northern Ireland [25–27]

According to the Anglia Cancer Network [28], the majority – 67.6% of patients – are diagnosed at stage III or IV. More people are diagnosed at an advanced stage. IV – 35.8%, than an early stage, with the smallest proportion of known-stage new cases presenting at stage II – 7.3%. One-year survival from lung cancer is strongly related to the stage of the disease at diagnosis. People at stage I have the highest survival rates – 71%. Survival is much lower for those diagnosed with stage IV disease – 14%. As expected, five-year survival of people diagnosed during 2003–2006 is lower than one-year survival across known stage groups. People presenting at stage I have the highest survival – 35%. Survival is lower for those diagnosed with stage III disease – 6%. Stage IV survival could not be calculated at five years due the small number of people surviving for more than two years.

In our study, the dominant stage in NSCLC is stage IV, 36.3%, followed by IIIA, 17.5%, stages IIIB and IIB, 13.6%, and so on. We registered a statistically significant association between survival and stage of NSCLC from diagnosis to the last check-up/death. In our study, 25% of the patients at stages IA and IB had survival rates from 15.8 m –16.1 m survival, those with stage IV disease – 9.7 m. The median survivals were: at stage IV – 5.2 m., IIIA and IIIB – 6.2 to 6.5 m., IA and IB – 6.8 to 7.8 m.

We registered a statistically significant association between survival and stage of NSCLC from the outset of treatment to the last check-up/death. Median survival from treatment outset to the last check-up/death is 5.4 m. The median survivals were: at stage IV – 4.1 m., IIIA and IIIB – 4.8 to 6 m., IA and IB – 7.4 to 8.3 m.

According to the number of survival rates calculated from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, based on people who were diagnosed with non-small-cell lung cancer between 1998 and 2000, people at stages IA and IB have the highest survival rates – 49% and 45%. Survival is much lower for those diagnosed with stage IV disease – 1% (5-year survival rate) [29].

The overall 5-year survival rate for non-small-cell lung cancer (all stages combined) is roughly 15%. The overall 5-year survival rate for stage 1 lung cancer is 60-80%.The overall survival rate for stage 2 lung cancer is 40–50%. The overall survival rate for stage IIIA lung cancer is 23%, but this varies widely among different cancers that are classified as stage IIIA. The 5-year survival rate with stage IIIB lung cancer is only 10%. The median survival time with treatment is 13 months. The overall 5-year survival rate with stage IV lung cancer is sadly less than 10%. The median survival time is about 8 months [21].

During the study we came to some interesting data, the median survivals in 2009, 2010 and 2011 differed from the diagnosis to the last check-up/death. Median survival in 2009 was 7.5 m and we registered a statistically significant longer survival compared to 2010 – 6.1 m, and in 2011 – 5.4 m. During 2009, 25% of patients survived for more than 15.9 m, which is a longer survival time compared with 2010 and 2011. (25% –11.5% and 25% – 8.8 m) (Graph 2).

Similar data and conclusions are received in calculating the survival from therapy to the last check-up/death. Median survival in 2009 was 6.2 m and it is a statistically significantly longer survival period compared with 2010 (5.9 m) and 2011 (4.6 m). During 2009, 25% of patients survived for more than 14.9 m, which is a longer survival time compared to 2010 and 2011 (25% – 12.3 m. and 25% – 8.3 m).

Conclusions

The results indicate that compared with international data our patients with NSCLC had a

shorter life of survival. Perhaps the reason is the high percentage of stages IV, IIIA and IIIB recorded in patients; the chances of longer survival are much greater if patients are detected at earlier stages.

Our findings in a survey regarding prevalence and survival in relation to the subtype of NSCLC-adenocarcinoma and planocelullar are different from global research. According to world literature, longer survival times have been recorded in adenocarcinoma subtype, while in our study, patients with subtype planocelullar had a longer survival time.

We hope that this study will help to improve the future treatment of non-small-cell lung cancer patients through optimizing the treatment for every single patient, which will help in longer patient survival. It can be concluded that today it is possible and necessary to individualize treatment of lung cancer in the Republic of Macedonia by introducing EGFR mutation testing as standard diagnostic practice and selecting patients according to EGFR mutation status, EGFR mutation positive and negative. EGFR mutation-positive patients should start initial treatment with EGFR-TKIs because personalized therapy with EGFR-TKIs (erlotinib) provides a greater survival benefit for this subgroup of patients and improves patient outcomes.

Precise determination of these data provides proper selection of the best treatment option and optimized therapy for every patient.

Glossary of Abbreviations

Progression-free survival ----------PFS
Overall survival ----------OS
World Health Organization----------WHO
Non-small-cell lung cancer----------NSCLC
Best supportive care----------BSC
Median survival time----------MST
Epidermal growth factor receptor----------EGFR
Epidermal growth factor receptor-tyrosine kinase inhibitors----------EGFR-TKIs
Year----------y
Months----------m
UCRO-----University Radiotherapy and Oncology Clinic

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Резиме

ЕПИДЕМИОЛОШКА АНАЛИЗА НА ПРЕЖИВУВАЊЕТО БЕЗ ПРОГРЕСИЈА НА БОЛЕСТА (PFS) И СЕВКУПНОТО ПРЕЖИВУВАЊЕ (OS) КАЈ ПАЦИЕНТИТЕ СО НЕСИТНОКЛЕТОЧЕН КАРЦИНОМ НА БЕЛИ ДРОБОВИ ВО РЕПУБЛИКА МАКЕДОНИЈА

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Карциномот на белите дробови претставува водечка причина за смртност од рак во светот, приближно 1,2 милиони смртни случаи секоја година. Подобрување на преживувањето од карцином на белите дробови е голем предизвик за современата онкологија, со оглед на тоа дека 5-годишното преживување останува < 15%, во сите фази на болеста и со < 7% кај пациентите со 10 години по дијагнозата. Околу 85 до 90% од ракот на белите дробови е неситноклеточен карцином на белите дробови (non-small cell lung cancer NSCLC). Карциномот на белите дробови е водечка причина на морталитетот во Македонија со повеќе од 900 нови дијагностицирани пациенти годишно (18). Мотивот за изработка на студијата е токму недостатокот на соодветни статистички податоци за третманот, резултатите и стапките на преживување на NSCLC пациенти во земјата. Главната цел е да се обезбеди процена на PFS и OS кај пациенти, лекувани на УКРО – Скопје, за период од последните три години: 2009–2011 година. Истражувањето претставува студија на следење. Студијата се темели на исполнување формулари за епидемиолошки анализа на PFS и OS кај NSCLC пациенти. Овие формулари содржат демографски, клинички и хистолошки податоци, како и датумите на дијагноза, третман и исход. Податоците се прибираат преку регистрација на секој пациент со NSCLC третиран во испитуваниот период. Статистичките серии се анализираат со одредување на стапки, пропорции, хи-квадрат и студентов т-тест и анализа на преживување. Во студијата беа вклучени 1002 пациенти со NSCLC лекувани на УКРО, од кои 859 беа мажи и 137 беа жени, а за 0,6% недостасуваат податоци за полот. Просечната возраст на пациентите беше 60,4 ± 9,0 г.,

минимум на 19 г., максимум од 85 г. Поголемиот дел од пациентите беа пушачи – 86,9%. Доминантната фаза во испитуваната група е стадиум IV со 36,3%, следен од IIIA 17,5%, IIIБ и IIБ стадиум со 13,6% и така натаму. Во испитуваната група на пациенти најчестиот поттип беше планоцелуларен карцином со 56,9%, 28,2% со аденокарцином (големи клетки) со 7,7% и непознат поттип со 7,2%. Медијаната на преживување од дијагнозата до последната контрола/смрт е 6,2 м. 25% од пациентите со NSCLC од дијагнозата до последната контрола/смрт умираат првите 2,5 м., а 25% преживуваат повеќе од 11,1 м. Медијаната на преживување од третманот до последната контрола/смрт е 5,4 м. 25% од пациентите со NSCLC од поставувањето на третманот до последната контрола/смрт умираат првите два месеци и 25% преживуваат повеќе од 10,8 м. Во текот на студијата се регистрираше дека медијаната на преживување во 2009, 2010 и 2011 година беше различна од дијагнозата до последната контрола/смрт. Во 2009 г., медијаната на преживување изнесуваше 7,5 м., се регистрираше статистички сигнификантно подолго преживување во споредба со 2010 г. – 6,1 м и 2011 г. – 5,4 м. Слични податоци и заклучоци се добиени и со пресметувањето на преживувањето од терапијата до последната контрола/смрт. Медијаната на преживување во 2009 г. изнесува 6,2 м., а тоа е статистички сигнификантно подолго преживување во споредба со 2010 г. (5,9 м) и 2011 г. (4,6 м). Резултатите укажуваат на тоа дека пациенти со NSCLC во споредба со меѓународните податоци имаат пократко време на преживување. Се надеваме дека оваа студија ќе помогне во иднина да се подобри третманот на NSCLC пациенти преку оптимизирање на лекувањето за секој пациент, кое ќе помогне во подолгото преживување на пациентот. Прецизното одредување на овие податоци обезбедува правилен избор на најдобар третман воедно и оптимизирана терапија за секој пациент.

Клучни зборови: non-small cell lung cancer, епидемиологија, преживување.

Table 1

Distribution of gender, age, smoking, stage, subtype, average time from diagnosis-treatment and diagnosis-last check-up

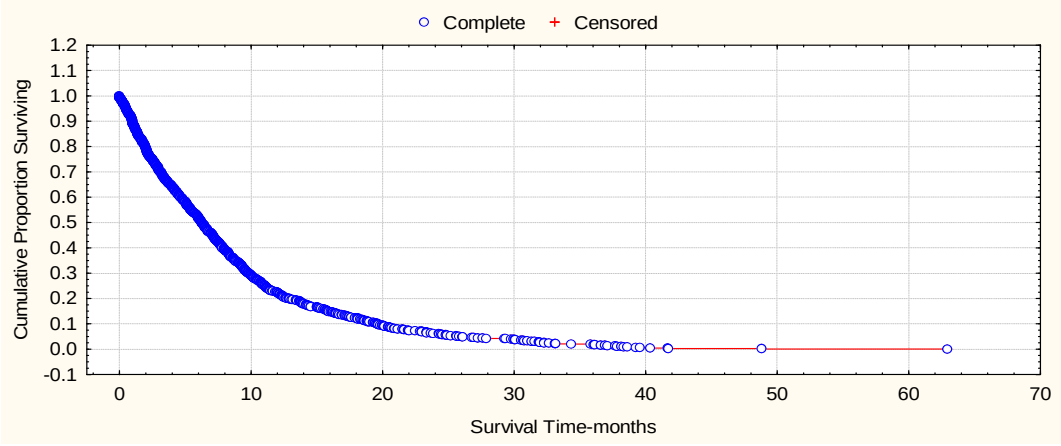
sex		**n (%)**		
Men		859(85.7)		
Women		137(13.7)		
Missing		6(0.6)		
average of age	60.4 y -mean	minimum 19 y	maximum 85 y	± St.Dev. 9.0
Men	60.8 y -mean	minimum 19 y	maximum 85 y	± St.Dev. 8.9
Woman	57.5 y -mean	minimum 33 y	maximum 74 y	± St.Dev. 8.8
Smoking	**yes** n (%)	**no** n (%)	**missing** n (%)	
total	871(86.9)	51(5.1)	80(8.0)	
Men	790(92.0)	13(1.5)	56(6.5)	
Women	80(58.4)	38(27.7)	19(13.9)	
Stage NSCLC		**n (%)**		
IA		12(1.2)		
I B		72(7.2)		
IIA		54(5.4)		
IIB		136(13.6)		
IIIA		175(17.5)		
IIIB		136(13.6)		
IV		364(36.3)		
Missing		53(5.3)		
Subtype NSCLC		**n (%)**		
planocelullar		570(56.9)		
adenocarcinoma		283(28.2)		
Large cell		77(7.7)		
missing/no closer subtype		72(7.2)		
With wife/husband				15(22,7)
Average time diagnosis-treatment				
1.3m -mean	minimum 0.03 m	maximum 31.5 m	± St.Dev. 2.3	
Average time diagnosis-last check up/death				
8.5m -mean	minimum 0.0 m	maximum 62.9 m	± St.Dev. 8.9	
patients who reached		**n (%)**		
Therapy		995(99.3)		
I progression		357(35.6)		
II progression		87(8.7)		

Table 2

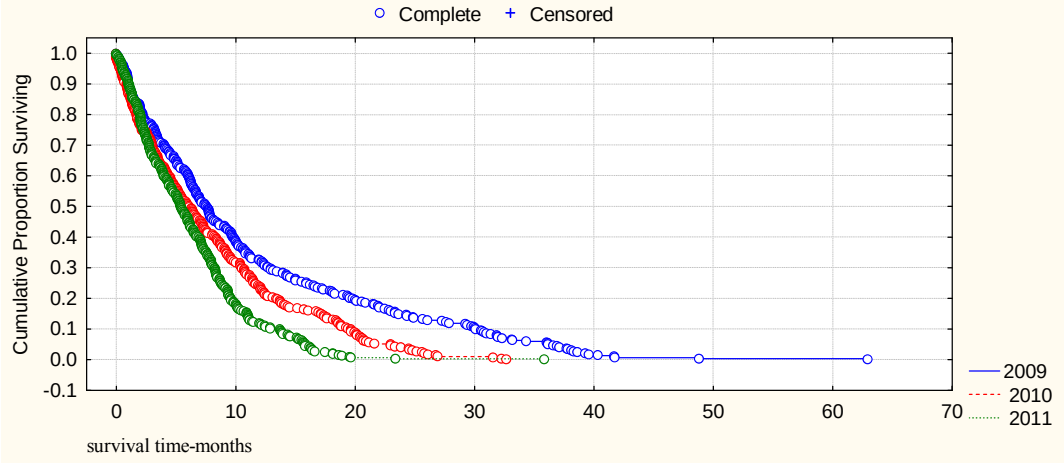
Proportional hazard (Cox) regression

N = 1002	Beta	Standard error	t-value	Exponent beta	Wald statistic	p
age	0.073102	0.036602	1.99719	1.075840	3.98879	0.045813
gender	-0.117325	0.104158	-1.12641	0.889296	1.26880	0.260001
smoking	-0.289238	0.164440	-1.75893	0.748834	3.09383	0.078599
stage	-0.082800	0.015726	-5.26513	0.920535	27.72156	0.000000
subtype	-0.016404	0.052158	-0.31451	0.983730	0.09891	0.753138

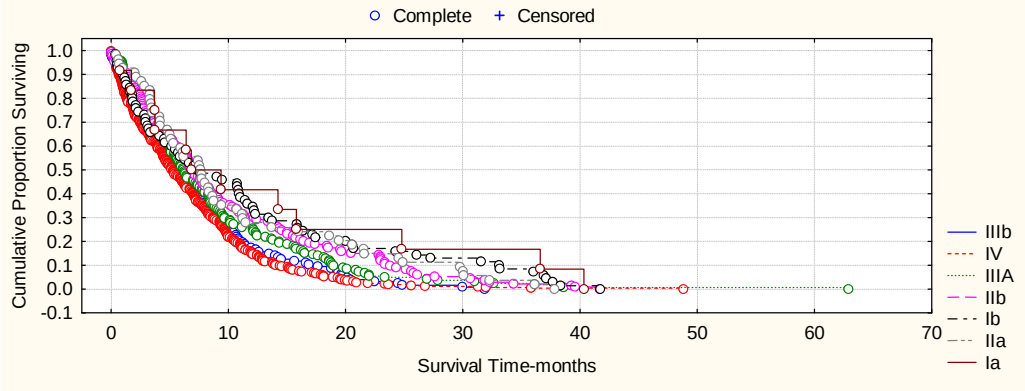
Graph 1 Kaplan-Meier curve of overall survival from diagnosis to last check-up/death



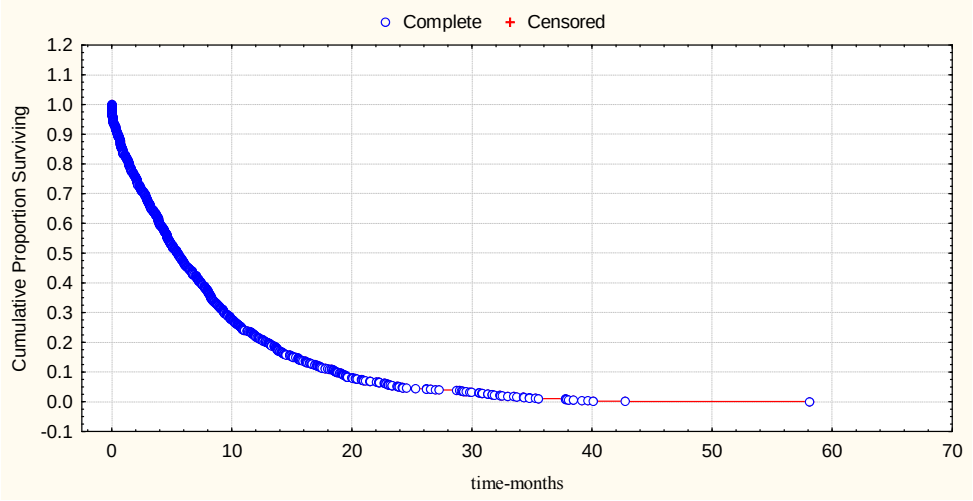
Graph 2 Kaplan-Meier curve of overall survival from diagnosis to last check-up/death by year of diagnosis



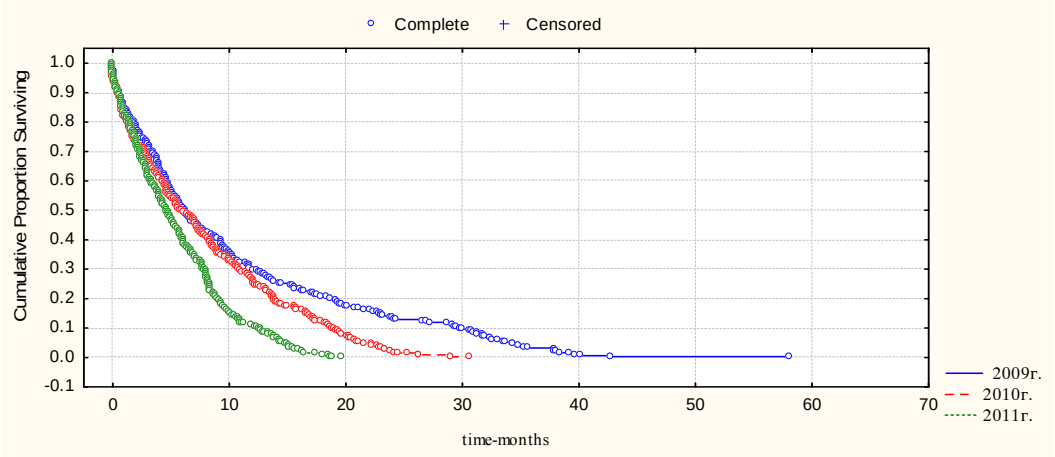
Graph 3 Kaplan-Meier curve of overall survival from diagnosis to last check-up/death by stage



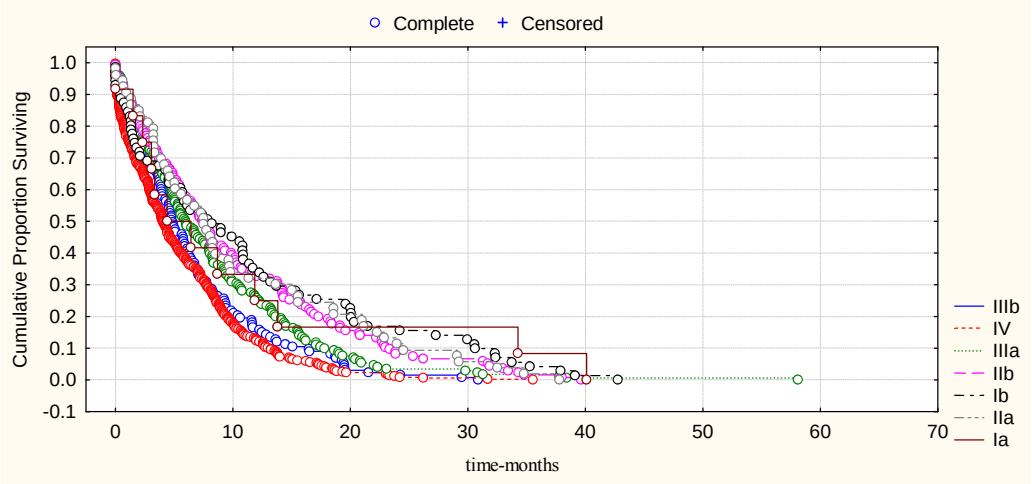
Grapf 4 Kaplan-Meier curve of overall survival from treatment to last check-up/death



Graph 5 Kaplan-Meier curve of overall survival from treatment to last check-up/death by year of diagnosis



Graph 6 Kaplan-Meier curve of overall survival from treatment to last check-up/death by stage



Graph 7 Kaplan-Meier curve of overall survival from treatment to last check-up/death by subtype