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Dissertation

Factor "Time" - Is it Significant for Lung Carcinoma?

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Abstract

Lung cancer is a global medical problem, with rising incidence and with 5-year survival of 5 - 10%. The aim of this work is to investigate whether waiting times and delays in diagnosis and treatment of patients with lung carcinoma have any bearing on prognosis and survival.

Investigation was performed in the Special Hospital for Lung Diseases and Tuberculosis, Brezovik. The study included all cases with diagnosis of lung carcinoma in 2014 in the Republic of Montenegro, in a total of 206 patients, with follow-up until the end of 2015.

Median age was 66, median Karnofsky score 80, sex ratio 5M:1F. Diagnostic procedure was bronchoscopy in 89% of patients. Histological type was SCLC in 25.7%, NSCLC in 74.3% of cases. Surgery was the main treatment for 24.4% of patients. Median delay from first symptoms to diagnosis of LC was 10.35 weeks - median 8 weeks (median patient's delay was 6.20 weeks, doctor's delay in PHC - 2.07, and in pulmonology services - 2.37 weeks). Median survival time for all patients was 39.27 weeks, median 34. There was no statistically significant difference between patient's delay/doctor's delay/total delay and the stage of lung carcinoma at the moment of diagnosis, treatment choice and survival. Our results indicate that longer delay is not associated with a poorer prognosis of lung carcinoma. Possible ways of reducing mortality of LC is prevention by lowering smoking incidence and improved therapeutic options.

Keywords: *Lung Cancer; Delay; Survival*

Introduction

Lung cancer is a major medical problem, with rising incidence and with 5-year survival of 5 - 10%. Apart from prevention, oncology pays most attention to early detection of carcinoma, which is expected to result in a better prognosis for malignant diseases and better survival prospects. In case of lung carcinoma, mass screenings including periodic chest X-rays and sputum cytology have resulted in a modest increase in the number of operable patients, but have not reduced mortality rate. There was even no prolongation of survival of statistical significance. Poor lung cancer prognosis is a consequence of the aggressive biological nature of lung carcinoma and comparative inefficiency of the current treatment methods. The effects of treatment on the course of these malignant diseases, including the latest treatment methods, are marginal. The focus should, therefore, be placed on the prevention - anti-smoking activities. However, since the most frequent localization of malignant disease in the world is in question (over 65 years of age), the possibilities of efficient detection of early-stage lung carcinoma are being investigated again. Rich countries are evaluating the importance of periodic chest CT scan, especially with peripheral lung carcinoma. With central tumours, immunofluorescent bronchoscopy and other expensive and borderline experimental methods are used in small series.

According to the available data, the lung carcinoma incidence rate in Montenegro had a steady growth between 1978 and 2005, with an average annual increase of 6%. The number of new patients - lung carcinoma incidence rate - had a steady growth between 1978 and 2005 in Montenegro, with an average annual increase of 6%. In male population, the incidence rate rose from 19.6/100,000 to 48.5/100,000, with an average annual growth of 5.8%. An average standardized incidence rate was 39.2/100,000 in male population. Between 1976 and 2005, the lung cancer mortality rate in Montenegro increased from 19.4 to 26.3/100,000, with an average growth rate of 2%. According to our statistics, around 300 citizens Montenegro are diagnosed with this disease every year.

Apart from prevention, oncology pays most attention to early detection of carcinoma, which is expected to result in better prognosis in several different tumour localizations. Unfortunately, with lung carcinoma, the research has not given the expected results so far. The problem of detection of early-stage disease is becoming increasingly topical. Nowadays, the importance "time factor" in the lung cancer diagnostics is examined through new medical methods. In that respect, "patient's delay" and/or "health care delay" are evaluated separately. In case of lung carcinoma, the effect "delay" on survival remains a great mystery. The previous studies suggest that both diagnosis and the beginning of treatment should be done as soon as possible.

The treatment delays are a constant problem. With the lung carcinoma treatment, the knowledge concerning the potential effect of delay on survival is not at a satisfactory level. Surgical treatment of early-stage (I, II) NSCLC patients could result in a 5-year survival of up to 75 - 80%, while there is no data that early treatment of non-resectable advanced NSCLC can affect the prognosis and survival [1]. The overall influence of delay in diagnosis of NSCLC on survival remains poorly understood [2]. It seems that the delay in NSCL patients is often longer than expected in the clinical practice. According to some studies, delay has a negative impact on prognosis [4-7], while other did not show such a correlation [3].

Having been interested in the effect of delay on diagnostics, treatment and survival of the lung cancer patients, we conducted a systematic, computer, biographic research of Pub Medline, using the key words lung carcinoma, delay and lung carcinoma, and lung carcinoma and delay. In this way, 16 studies were identified, as well as the subject of this research. The authors evaluated the studies independently, using the prepared grading form, including the number of patients, cancer stage, and delay in both NSCLC and SCLC patients.

The time intervals between the onset of symptoms and diagnosis and the beginning of treatment of a patient could be divided into "patient's delay" and "doctor's delay". Patient's delay is the time between the first symptoms and the first contact with the medical workers. The doctor's delay is defined as a time interval between the first examination at the health care institution and the beginning of treatment or a decision that the cancer specific treatment is not possible.

The above studies show great variations in time intervals between the recognition of first symptoms and the first contact with doctor. The shortest interval was reported in Italy, by the G.I.V.I.O study, according to which an average delay of 7 days was reported in 20 to 35 surveyed hospitals [3]. According to the research conducted by Moore*., et al*. in the United States of America, a delay of over three months was observed in 25% of patients. The longest delay, of an average of four months, was noticed in the studies including the patients, aged under 45, from the USA [4]. Unfortunately, most of the T1 tumours are asymptomatic, and when the first symptom is noticed, the disease is already at an advanced stage, either at T3-4 or N1, 2, 3.

According to a study by Ode., *et al.* based on 409 surgically treated patients with non-small cell lung cancer, the incidence of N1, 2, 3 status was 0% in under 10 mm tumours, 21% in tumours between 11 and 20 mm, 23% in tumours between 21 and 30 mm, 48% in tumours larger than 300 mm.

There are great variations in the intervals between the first contact with doctor and the established diagnosis. According to the Swedish study by Christensen ED*., et al.* [2], the availability of general practitioners has decreased in the last several years, resulting in long waiting lists. The first doctor's delay was seen at the level of general practitioners and it amounted to 56 days.

The most frequent causes were waiting for the lung roentgenogram and late referral to a specialist. A shorter delay by general practitioners was referred to in the Italian study by Encuentra L., *et al.* [3] and the availability of a family doctor, who can refer a patient to the chest computed tomography is mentioned as an explanation of the shorter delay. In the literature, different delays were used reflecting different goals. The study by Billing and Wells [9], defines the total delay as a period between the first visit to the general practitioner and surgery, giving further divisions into sub-groups according to the reasons of delay. According to the study by Christensen., *et al.* the endpoint is the date when a patient is either operated on or considered inoperable [3].

The tumour could spread considerably during a delay. The time interval between the first neoplastic changes in the bronchial epithelium and the first symptom is very long. It is considered that a tumour growth from Tx to T1, T2 is not just a local growth of tumour but also an increase in its metastatic potential, meaning that there is more chance that N increases with an increase of T, same as M0 in M1. In the study by O'Rourke and Edwards [6], the NSCLC patients referred for radiotherapy initially had a diagnostic CT scan and later a radiotherapy planning CT scan. Delay between the two CT scans amounted to 18 - 131 days (median 54 days) and tumour growth in terms of percentage change in tumour cross-sectional area ranged from 0 to 373%, with a median increase of 19% in the time interval passed. In the period between the two CT scans, six patients became clinically incurable. The study suggests that the patients with squamous cell carcinomas will be at high risk of progression while waiting [6].

According to the authors Jensen RA, Mainz J and Overgaard J [7], six studies, including 959 patients (range 29 - 410), analysed correlations between time interval and stage at diagnosis, stage at surgery or survival [5,7-11]. Only one of the studies [8] focused on the association between delay and survival. According to this study, a significantly better rate of survival was found in patients with longer patient's delay than in those with longer doctor's delay [9]. According to another study by Deslauries J., *et al.* six out of 29 patients became clinically incurable while waiting for treatment [10].

Koyi H*., et al.* analysed the results of a 5-year research including 750 NSCLC patients at the Uppsala and Vastmanland regional centre in central Sweeden.[9] The effect of delay and its significance as the prognostic factor was studied.

The patients who did not receive cancer specific treatment were excluded from the study, which focused on 466 patients who were treated with chemotherapy, radiotherapy or surgery. All NSCLC patients were registered at the Regional Oncology Centre in Uppsala. The centralised database of all patients enabled a better data management, correction and control of the achieved results. The data on histopathologic-type tumour, staging and treatment completed were obtained from the ROC database. Additional clinical data on individual patients was collected retrospectively from the patient records kept by the Uppsala University Hospital and the Vastmanland Country Hospital, which had completed all diagnostic examinations. The data revealed that: the date of first symptoms in NSCLC patients, the date of first consultation with a pulmonologist, the date of the beginning of and the type of oncologic treatment. The procedures used for staging are chest and upper abdominal CT scan, bronchoscopy, mediastinoscopy, abdominal ultrasound, bone scintigraphy and laboratory tests.

Two types of delay were analysed:

1. Patient's delay, defined as a time interval from the onset of first symptom of disease to the beginning of treatment, and
2. Doctor's delay, defined as a time interval from the first consultation with doctor to the beginning of treatment.

The date of the appearance of first symptom was known for 76% of the patients (n = 354), while the date of the first consultation with pulmonologist was known for 89% of them (n = 413). The date of the beginning of treatment was known for all 466 patients. The statistical methods used included data analyses for all patients (n = 466), including age, sex, histological type, disease stage, and type of treatment. In addition to median delay for all subgroups, the parametric tests were also included for irregularly distributed data. The Mann-Whitney test and the Kruskal-Wallis test were used for the multiple group analysis. The differences in delay were considerable if $p \leq 0.05$. The examined survival time was calculated according to the "life table" method for all patients. The results were presented for 268 male patients, aged 65.8 on average (43.6 - 86.2), and 198 female patients aged 63.9 on average (39.3 - 89.3). Two most frequent histological types of lung carcinoma were adenocarcinoma (42%), and epidermoid carcinoma (33%). Hundred and fifty-one patients were surgically treated (101 underwent only surgery, 37 adjuvant chemotherapy, 8 received post-operative radiotherapy, while 5 received both chemotherapy and radiotherapy). Out of 315 patients who did not surgically treated, 143 received systemic chemotherapy, 99 received radiotherapy, while 73 patients received both chemotherapy and radiotherapy [10].

The work by WM Alberts*., et al.* examines the causes of unnecessary doctor's delay [11]. According to them, one of the major reasons is the lack of comprehensive multidisciplinary approach to treatment of patients with lung carcinoma. With the establishment of multi-disciplinary clinics (councils), the doctors of different specialities (pulmonologists, lung surgeons, lung oncologists, radiotherapists, pathologists, psychologists) would make treatment decisions all in one place, using the latest treatment expertise in the best possible way. In that way, it would be easier for doctors to plan the treatment, reducing the unnecessary delay between family doctor and specialists. The recommendations of the *British Thoracic Society* on the time intervals for evaluation, diagnostics and treatment are aimed at providing guidelines and good practice for treating a patient with lung carcinoma [12,13].

According to these guidelines: All patients should be examined no longer than one week from the referral from the home doctor; Diagnostics must be completed no later than two weeks from the date when lung carcinoma was suspected; Chemotherapy must start no longer than seven days after the council's decision on that type of treatment; Radiotherapy should start no longer than two weeks after the decision has been made for urgent cases, and no longer than four weeks after the decision has been made for complicates cases, while waiting time for palliative radiotherapy should be no longer than two weeks. Surgical intervention (operation) should be completed within four to eight weeks after the treatment decision has been made [14].

Objective of the Research

Scientific objective i.e. the main contribution of this study is to examine the correlation of delay and the survival of patients with lung carcinoma.

The hypothesis for this carcinoma localization is that the delay factor has a limited significance, i.e. it has no bearing on the lung carcinoma mortality.

The research is expected to provide answers to the following questions:

- If the patient's delay and/or doctor's delay, as well as the total delay have any bearing on length of survival of the lung cancer patients.
- What is the real prognostic significance of delay for lung cancer.
- What recommendations could be issued in order to improve the outcome of treatment of lung cancer patients, at what level should the efforts be focused on, in order to raise the awareness of patents and civil society, and improve coordination within the health service.

Respondents and Methodology

The subject of the research was the effect of delay on the lung carcinoma prognosis, focusing on the total delay, patient's delay, and health service delay, including the relations between the doctors of primary health care and specialist service, as well as the time interval from diagnosis to the beginning of any type of treatment of the primary malignant process in the lungs. At the Special Hospital for Lung Diseases and Tuberculosis in Brezovik, the institution in charge of lung carcinoma diagnostics and treatment at the state level, approximately 200 - 250 new lung carcinoma patients are diagnosed every year. In the last several years, this number has seen a steady growth.

With the adoption of the Law on Limited Use of Tobacco Products (2004), a comprehensive campaign was initiated, aimed at lowering the number of lung carcinoma patients. Unfortunately, according to the statistical data, there are still no results of the undertaken measures. This retrospective study includes all lung carcinoma patients hospitalized at the Special Hospital for Lung Diseases and Tuberculosis "Brezovik" in Niksic, over a 12-month period (2014), with the a 12-month follow-up after the inclusion of the last patient in the study.

The study included a total of 206 lung carcinoma patients, who were diagnosed and treated between 1 January and 31 December 2014, and monitored for the following 12 months until the end of 2015.

Results of the Research

In compliance with the methodology used, our study included 206 patients, diagnosed and treated in 2014 at the Special Hospital for Lung Diseases and Tuberculosis in Brezovik - Montenegro. Lung carcinoma is a disease of middle-aged men, with a peak incidence in the seventh decade of life. In the last two decades, a sudden growth was seen in the number of female lung carcinoma patients, associated with an increase in the number of female smokers. According to gender analysis, most of the patients included in our study were men - 171 (83.0%), while only 35 (17.0%) were women, with the gender ratio of 5M:1F.

Having analysed the group of patients according to their smoking habits, we concluded that out of 206 patients, 167 were smokers (81%), 75% of whom were heavy smokers (140 out of 206). An average smoking history amounted to 29.4 years, with a daily average of 29.17 cigarettes smoked.

Patient's delay

Conducting a patient survey concerning the first symptoms of the disease and their recognition until their consultations with doctors (patient's delay), we found that this time interval ranged between 2 - 3 days and 33 weeks, with an average of 6.2 weeks (between 0.23 and 33.00, with a 95% confidence interval for a group of 206 patients) or median 4.00 weeks (with a 95% confidence interval). Having examined the medical records and consulted the patients, we noticed that an average of 6.52 weeks elapsed between the onset of first symptoms and chest radiography (between 1.00 and 34.00 weeks with a 95% confidence interval).

Doctor's delay I

The average doctor's delay in the primary health care until the examination by a lung disease specialist is 2.07 weeks (between 1.00 and 20.00 weeks with a 95% confidence interval). The Special Hospital for Lung Diseases "Brezovik" is a central institution for diagnostics and treatment of lung carcinoma in Montenegro, which means that almost all patients were treated there. The decisions on the manner of treatment of the lung cancer patients are taken by a council. In most cases, the PH results are obtained after the bronchoscopy. In few patients, a malign lung disease is diagnosed after a surgery (VATS, Wedge resection) performed in the chest surgery department of the Podgorica Clinic. An average delay of the specialist medical service is 2.37 weeks.

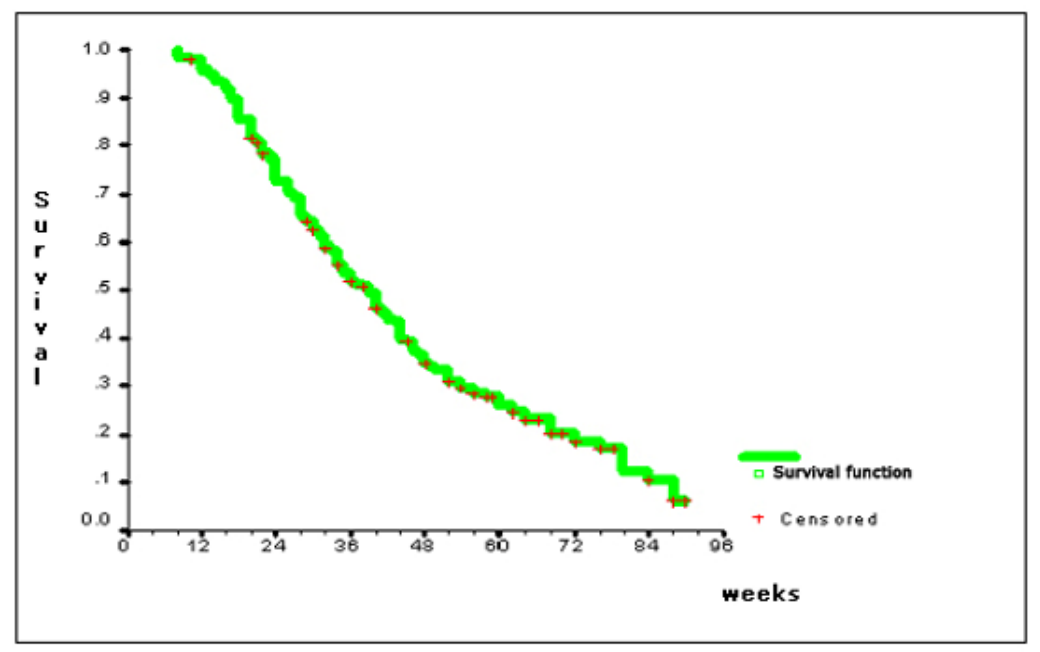
Doctor's delay II

Having added together the doctor's delay by the primary health care (I) and the one by the specialist medical service (II) before the primary lung carcinoma was diagnosed, we concluded that the healthcare delay or the total doctors' delay was 4.22 weeks (between 1.00 and 23.00 weeks with a 95% confidence interval).

Total delay

Adding together the patient's delay and the health care delay, we get an average total delay of 10.35 weeks. For the whole group of 206 patients surveyed, median delay amounted to 8.0 weeks (between 2.00 and 51.00 weeks with a 95% confidence interval).

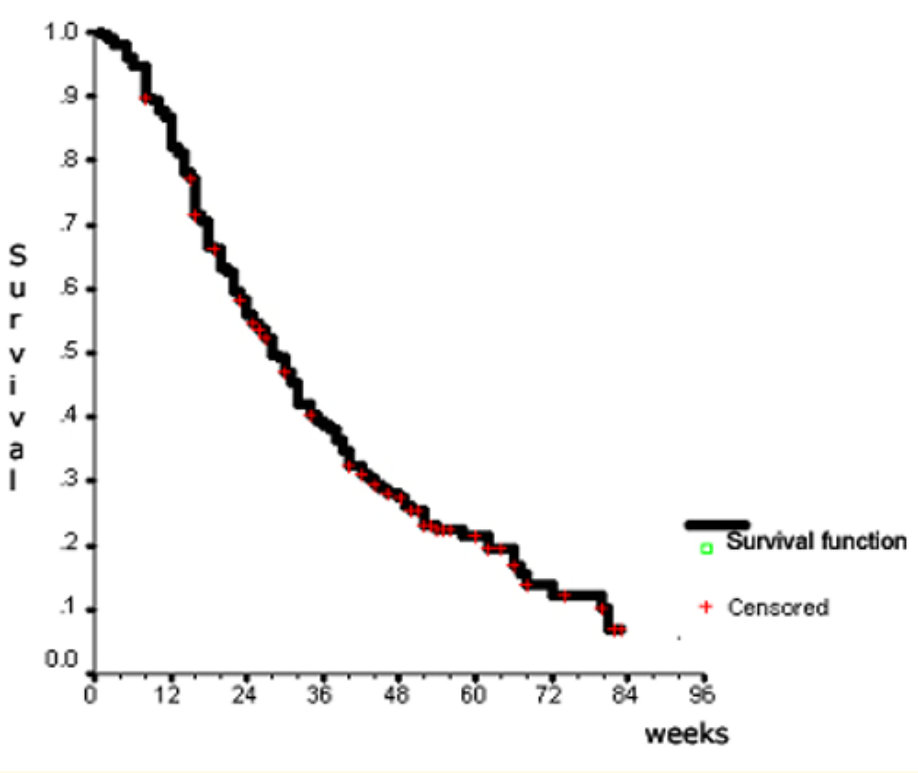
We completed a Kaplan - Meier analysis of survival for the group of surveyed patients in relation to the period between the onset of first symptoms and the end of research.



Graph 1: *Survival curve after the onset of first symptoms (Kaplan - Meier).*

According to the statistical analysis based on the Kaplan-Meier method, it is evident that the cumulative survival is 12 weeks after the onset of first symptoms, with a 95% confidence interval. An average survival time was 44.17 weeks, between 40.66 and 47.68 weeks with a 95 percent confidence interval. Median survival was 39 weeks, between 34.32 and 43.68 weeks, with a 95% confidence interval.

According to a statistical analysis based on the Kaplan-Meier method, an average survival after the disease was diagnosed was 35.48 weeks, between 31.94 and 39.02 weeks with a 95% confidence interval. Median survival was 28 weeks, between 24.02 and 31.98 weeks, with a 95% confidence interval.



Graph 2: *Survival curve after diagnosis (Kaplan - Meier).*

Survival in relation to patient's delay under and over 8 weeks

In compliance with the task of the study, we divided the patients into two separate groups: the patients who recognized their symptoms and consulted doctors within eight weeks and the patients with a delay longer than 8 weeks, and analysed their survival.

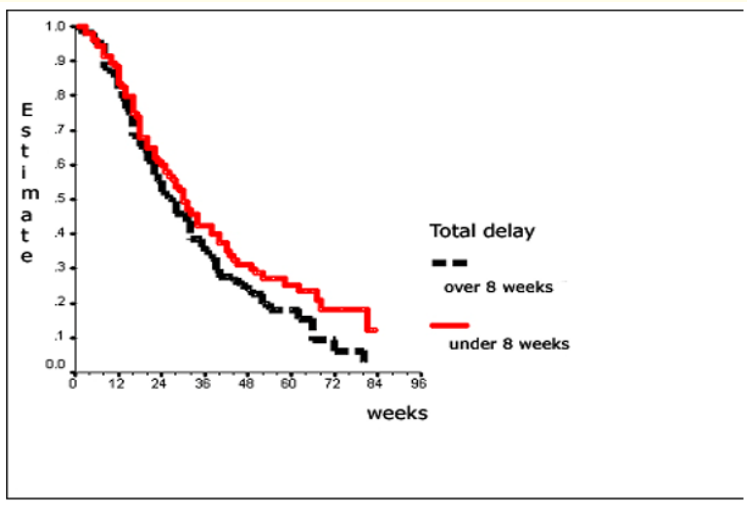
The group of patients with a delay shorter than eight weeks included 104 out of 206 patients. Median survival of the group with shorter delay was 35.00 weeks (95% CI: 29.86 - 40.16), while median survival for the group of patients who recognized their symptoms and consulted doctors after 8 weeks was 40.00 (95%CI: 33.07 - 46.93).

There was no statistically significant difference in survival of group in relation to patient's delay ($p > 0.05$) under and over 8 weeks.

We analysed the survival in relation to delay between the onset of first symptoms and the diagnosis, patient's and doctor's delay. We divided the patients into two groups: the patients who were diagnosed within eight weeks and the patients who were diagnosed eight weeks after the onset of first symptoms.

The group of patients diagnosed within eight weeks included 30 out of 104 live patients. Median survival of the group of patients diagnosed within eight weeks was 30.00 weeks (95% CI: 24.82 - 35.18), while median survival of the group of patients diagnosed after eight weeks was 27.00 (95% CI: 20.44 - 33.56).

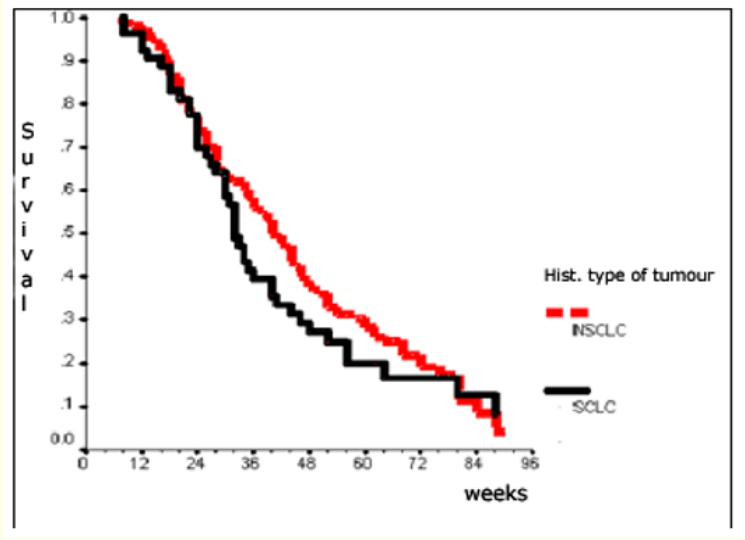
There was no statistically significant difference in survival of group in relation to patient delay ($p > 0.05$) under and over 8 weeks.



Graph 3: *Survival curve in relation to patient's and doctor's delay (Kaplan - Meier).*

In our study, survival of the SCLC patients ranged between 33.83 and 47.26 weeks after the onset of first symptoms, with median survival of 32.00 weeks. For the group of NSCLC patients, survival ranged between 41.31 and 49.47, with median survival of 40.00 weeks for the log rank 1.16 and $p = 0.2810$ (Graph 4).

There was no statistically significant difference in survival in relation to PH type of disease ($p > 0.05$).



Graph 4: *Survival curve after the onset of first symptoms in relation to PH type - SCLC/NSCLC (Kaplan - Meier).*

In our study, survival of SCLC patients ranged between 25.73 and 37.88 weeks, with median survival of 25 weeks.

In the group of NSCLC patients, survival ranged between 32.52 and 40.987 weeks, with median survival of 30.00 weeks for the log rank 1.42 and p = 0.2334.

There was no statistically significant difference in survival after the disease was diagnosed in relation to PH type of disease (Mann-Whitney test u = 3.667; z = 0.972; p > 0.05).

Discussion and Conclusion

In the last several years, the studies based on the effect of delay factor on the course and prognosis of the disease came into focus. One of the ethical and social problems in the healthcare system are long delays between the time the disease was diagnosed and the beginning of treatment of the patients with lung carcinoma. It is generally accepted (supported by some publications and disputed by others) that a longer delay in the beginning of treatments of patients with carcinoma results in a shorter survival, especially for tumours with bad prognosis such as the lung carcinoma.

The initial symptoms of lung carcinoma are not specific, meaning that there almost no warning symptoms. The patients with lung carcinoma could have different symptoms, the most frequent being coughing, coughing up blood, chest pain, shortness of breath, loss of appetite, weight loss, high temperature, insomnia, and bone pain. Many authors add disease stress to already wide palette of symptoms. Very often, the lung carcinoma symptoms are "masked" and it is sometimes difficult to recognize new ones, especially in patients with associated respiratory diseases, such as the chronic obstructive bronchitis. Moreover, demographic changes, growing number of female patients, adenocarcinoma, and young patients affect the symptomatic image of patients with lung carcinoma. An onset of only one symptom is often ignored by patients, which delays both diagnosis and treatment. The reasons for such behaviour of patients should be sought in their lack of understanding and information they have about the disease.

In their work published in the *Thorax* magazine, Corner., *et al*. [8] present the findings of their retrospective study, saying that they analysed over 30 different symptoms the lung carcinoma patients identified in their interviews on the onset of the disease. The most frequently mentioned symptoms were coughing and shortness of breath (15/22), while over one half of the patients had chest pains (12/22). Vomiting, depression, insomnia and weight loss were seen in over one half of the patients with advanced-stage disease. The authors say that all patients had at least one "new" symptom before the diagnosis. Median delay between the initial health changes and the first consultations with doctor was 7 months, with an additional 5-month delay until the disease was diagnosed. Not even such a long delay had any statistical significance. In this study, the authors found no difference in patient delay in relation to lung carcinoma stage and survival.

A large number of studies gave no answer to this question.

In our study, the most frequent symptoms were: chest pain in 79%, coughing in 84%, and weight loss in 82% of patients. The earliest sign that "made" patients consult a doctor, was coughing up blood, with median 2 weeks (95% CI: 1 - 12). An average duration of chest pain before consultation with doctor was 4 weeks (95% CI: 2 - 33). According to Beckles., *et al.* [15], in a smaller percentage of cases, initial radiography of patients with haemoptysis gave completely negative result. However, the authors recommend additional diagnostics suspecting a malign process, for all patients with haemoptysis younger than 40, regardless of their negative radiographic results. According to the literature, haemoptysis as a symptom is seen at presentation in 6 - 35% of patients. According to Beckles., *et al.* 6% of patients were asymptomatic at diagnosis, 27% of patients had respiratory symptoms, while 27% and 32% of patients had general symptoms and symptoms as a result of distant metastases respectively [15]. In our study, the disease was discovered by chance in 7 (3.4%) of cases, since they were respiratory asymptomatic. There were 15 (7.3%) patients with one symptom, while 50 - 55 (approximately 25%) patients most frequently had 3 - 4 symptoms. In our study, haemoptysis was an initial sign of disease in 15% of patients.

Median Karnofsky index was 80%.

A delay, or diagnostic delay, in the treatment of lung carcinoma patients is analysed through two time categories: the first is patient's delay, a time interval between the onset of first symptoms and consultation with doctor, while the second one is doctor's delay, or the time interval between the first consultation with doctor and the beginning of treatment of a malign disease. In the literature, the effect of delay on survival of lung carcinoma patients has been defined as unpredictable. Most of the studies started from an assumption that a shorter delay results in a better survival rate. However, some research results did not confirm this assumption. The results of the study by Myrdal G., *et al.* [2] show that not even longer patient's delay and longer doctor's delay were associated with worse prognosis and shorter survival. On the contrary, the prognoses were worse in patients with shorter delay. Moreover, the results of this study showed that the patients with limited disease had longer delay until they received cancer specific treatment than those with advanced disease. The references include the articles with the results of the research based on smaller series of patients, analysing the issue of delay in diagnostics and treatment in correlation with the stage of disease at diagnosis, progression of tumour from diagnosis to treatment, and the time for tumours to double their volume in relation to their histological type, both in SCLC and NSCLC. According to the observations of Salomaa E-R., *et al.* [16] the growth of NSCLC is based on the mathematical models, suggesting that it takes 10 to 15 years from the appearance of the first cancer cells to the possibility of detecting a NSCLC by conventional chest radiograph. According to the literature, the time observed for lung tumours to double their volume ranges from 4 to 56 weeks, with a median time of 17 weeks. This indicates that the growth of a tumour is comparatively slow [17,18]. Two studies monitored the growth of primary tumour with consequent CT chest scans, observing a great diversity in the time of tumour growth [19,20]. The previous studies have failed to answer the question when the metastasis of lung carcinoma starts [21]. According to the study by Jung KJ., *et al.* in patients with T1 lung carcinoma, extra-pulmonary metastases were found in 13% of patients at diagnosis, while distant metastases were found in 24% of patients one year later [19]. If metastases start growing years before the lung carcinoma has been detected, it is difficult to expect that the delay will have any prognostic significance [22].

Our study included 206 patients diagnosed with malign lung carcinoma in 2005. It included all lung carcinoma patients in Montenegro that year. In our research, lung carcinoma is a disease of middle-aged men, with a peak incidence in the seventh decade of life, most frequently found in heavy smokers. According to gender structure, 83% of patients were men and 17% women, with the gender ratio of 5(M):1(F). The youngest patient was a woman of 36 and the oldest one was 86, with median age of 66. Ten percent of patients were younger than 50, while 20% of them were over 70.

The distribution of patients in our study, according to gender and age, corresponds to the research of other authors. Our patients were of similar age, median 66, compared with median 65 in the American and 68 in Western European studies [18]. The gender ratio of disease is 1:3-4 on the American continent, while it is 1:5 in our study. If the number of women with lung carcinoma continues to grow, it is expected that, the lung carcinoma incidence in women will have exceeded the one in men by 2030. In terms of prognostic significance of radiographic localization of lung carcinoma, there was no consensus, with different results depending on the series [23].

In our study, the localization of primary tumour was equal for left and right lung (51:49), although the most dominant localization was in the upper right lobe, where tumours were diagnosed in 41% of our patients with lung carcinoma.

Having analysed the patient's delay, our study concluded that an average delay between the onset and recognition of first symptoms and presentation to doctor was 6.2 weeks (95% CI 0.23 - 33.0). The delay between the onset of first symptoms and the beginning of treatment amounted to 9.63 weeks (95% CI: 1 - 35.0).

After observing the patient's delay in relation to the pathohistological type of lung carcinoma, no statistical significance was found, since it amounted to 10.6 weeks in SCLC patients and 12.00 weeks in NSCLC patients (153 out of 206).

In comparison with the results of the Italian researchers presented in the G.I.V.I.O. study [24], which reported an average delay of 7 days, our research indicated a little longer delay, but it could be considered as a comparatively short delay in general, in comparison with the results of Myrdal G., *et al.* [2] reporting a 4.6 month delay, or Mood., *et al. USA* [15], which found a delay longer than 3 months in 25% of patients. The longest patient's delay was observed in the studies including the U.S. patients under 45, amounting to an average of 6 months.

Mackillop WJ., *et al.* [26] explain such a wide range of patients' delay by cultural and economic conditions in the places of research, as well as by the education level of the population surveyed.

In their study, Bowen., *et al.* [25] say that patient delay is longer in men. Over one half of them ask family and friends for support and encouragement to visit their doctor, while 75% of them are either not aware of the significance of symptoms or they were not identified. In their study, the authors attach great significance to a closer and frequent contact with doctor. They believe that an improvement of health education thorough training programmes focusing on lung carcinoma would reduce the delay between the onset of first symptoms and the first consultation with the primary health care doctors. In their work, Mydral., *et al.* [2] argue that the delay from symptoms to treatment is shorter in patients with stage IV lung carcinoma (median 3.4 months) than in the stage I and II patients (median 5.5 months). They explain this by the fact that the patients with advanced disease have more symptoms and signs of a disease compelling them to contact a doctor. The healthcare reform that has been going on in Montenegro in the last several years is aimed at establishing a closer communication between the healthcare beneficiaries on the one hand and the healthcare service on the other. The purpose of the "selected doctor" project, offering the possibility to every citizen to have their own doctor, is to enable the selected doctor to know their patients better and reduce doctor-patient barriers. A wide anti-smoking campaign and establishment of several non-governmental organizations dealing with this problem are aimed at educating as many people as possible about the diseases caused by this detrimental habit. In terms of doctors' delay, the results of research of the health service delay are very different. In the literature, different delays were used reflecting different goals.

In the work by Billing and Wells [9], total delay was defined as the time from the first visit to the general practitioner until surgery, and then further divided into subgroups in order to determine the reasons for the observed delay. In the work by Christensen., *et al.* [3] the end-point is the date when the patient was either operated on or considered inoperable. According to a Swedish lung carcinoma group, it is recommended to finish all diagnostic tests for 80% of patients within 4 weeks from the examination by a pulmonologist, while the cancer specific treatment should start within two weeks from the diagnosis. In the United Kingdom, it is considered that radical radiography should start within two weeks from the diagnosis [5]. In Canada, it is recommended that the interval between the examination by a selected doctor and diagnosis should be maximum 4 weeks, while the one between the diagnosis and surgery should be no longer than two weeks [27]. According to the retrospective study by Mydral G., *et al.* [2] the doctor's delay in one half of the NSCLC patients amounted to 2.5 months. The cancer specific treatment started within 6 weeks from the first consultation with a chest physician. Surgically treated patients had longer delay than those who did not have surgery. This was explained by long waiting lists for surgery in Sweden. The researcher proposed the establishment of multidisciplinary teams, including chest surgeons and oncologists. According to the research by Deegan*., et al.* median doctor's delay has been reduced to five weeks after the first consultation with a doctor [22]. In the research by Jensen*., et al.* [7] it was difficult to determine doctor's delay since several different points in treatment had passed. They say that the delay before treatment ranged from 48 to 189 days, with median delay of only 9 days from the first visit to the lung specialist to diagnosis.

In our study, doctor's delay includes the primary health care delay, and the secondary, i.e. tertiary health service delay (specialist services). In our case, the primary health care delay was 2.07 weeks (95% CI: 1.0 - 20.0), while the specialist services' delay was similar - 2.37 weeks. The total delay amounted to 4.22 weeks (95% CI: 1.00 - 23.00 weeks).

Comparing the results of our research with the ones from the literature, we can conclude that the doctor's delay was considerably shorter in our study. The reason for that could be sought in the centralization of health care in Montenegro and the role of councils in deciding on the treatment of patients with lung carcinoma. The first Malign Disease Council in Montenegro was set up in 1998 at the Brezovik hospital, and its purpose was to ensure a comprehensive examination of the lung carcinoma patients, reduce the possibility of patient's "wandering", and achieve better coordination among the doctors involved in the cancer specific treatment (oncologists, radiotherapists, and chest surgeons). The results of our research correspond to the recommendations of the British Thoracic Society, that the diagnostic process should be completed within the first ten days of the stay in our hospital, a decision on the beginning of chemotherapy should be made as soon as possible, no longer than seven days after the decision has been made, while the scheduled surgery is to be completed within four weeks at the Chest Surgery Clinic of the Podgorica Clinical Centre. Considering the total delay, including the patient's and doctor's delay, in the work by Billing., *et al.* the total delay until surgery amounted to 109 days in the NSCLC patients, including a month of patient's delay and two months of doctor's delay. The authors also argue that, in potentially operable patients, the length of delay is not in correlation with the tumour stage. In the conclusions of their study, Mydral., *et al.* [2] say that an increase in the total delay, including patient's delay and doctors' delay, has no negative effect on the survival, which proved to be true in patients with the stage III and IV lung carcinoma. They also argue that, in patients with the stage I and II lung carcinoma, which can be treated by radical surgery, a longer delay could have decisive bearing on their prognosis. In our study, when both delays i.e. patient's delay and health service delay are added together, the average total delay amounts to 10.35 weeks. For the whole surveyed group of 206 patients, median total delay amounts to 8.0 weeks (between 2.00 and 51.00 weeks with a 95% confidence interval).

The main parameter of success in the treatment of patients with malign disease is the survival. Adhering to the defined objectives, our study focused on determining if the delay had any bearing on the survival of patents with lung carcinoma. Having divided the delay into two components: patient's delay and doctors' delay, we tried to see the reasons for poor survival rate in patients with lung carcinoma in a more objective manner. Our intention was to identify the place where the mistakes are made, and try to influence their redress, in order to improve the chances of survival for the patients with lung carcinoma. During our research, we did not "lose" any patients, since all of them relied on a single health centre and a single Council, which gave us insight into the medical condition of each individual patient. We analysed the survival of our patients according to the Kaplan - Meier method, starting from two points:

1. Survival of patients with lung carcinoma from the onset of first symptoms.
2. Survival of patients with lung carcinoma from diagnosis.

In our study, a cumulative survival probability in relation to the onset of first symptoms was 12 weeks, with a 95% confidence interval. For the whole group, an average survival was 44.17 weeks (95% CI: 40.66 - 47.68). An average survival after diagnosis was 35.48 weeks (95% CI: 31.94 - 39.02).

There was no statistically significant difference in the survival of patients after the onset of first symptoms in relation to the histological type of lung carcinoma ($p > 0.05$), as well as in the survival of patients in relation to the moment when they were diagnosed with malignant disease ($p > 0.05$). Having analysed the survival in relation to the patient's delay shorter than eight weeks (shorter delay) and longer than eight weeks (longer delay), we observed no statistically significant difference ($p > 0.05$). Namely, median survival of the group with shorter delay was 35.00 weeks (95% CI: 29.86 - 40.16), while the one with longer delay was 40.00 (95%: 33.07 - 46.93). When we compared, using the same parameters (delay shorter and longer than eight weeks), the survival of patients in relation to the time when lung carcinoma was diagnosed, we also did not get any statistically significant difference ($p > 0.05$). Our results were identical to those of Aragoneses F., *et al.* [28] in the study including 1082 NSCLC patients. They did not observe any statistically significant difference in the survival in relation to histology of lung carcinoma, clinical stage, and the length of delay in any period, even when patients with the shortest delay of 1 to 20 days were compared with the ones with the longest delay of over 60 days. In the study by Salomaa E-R., *et al.* [16] of 2006, including 133 patients with lung carcinoma, the total survival was 31% after the first year and 20% after the second one. They divided

patients into two groups: patients with a delay longer than or equal to the median time, and patients with a delay shorter than the median time. Patients with a delay longer than the median time had a 40% lower risk of dying compared with the patients with a shorter delay (HR 0.60; 95% CI, 0.39 - 0.91; p = 0.020). The result was similar whether they used the delay time from the first symptoms to treatment or from the first visit to a doctor until the beginning of treatment. Patients with longer delays had a better prognosis. There was also no significant interaction between the disease stage at diagnosis and the delay. The prognostic difference between patients with long and short delays was seen in patients with advanced disease, stage IIIb to IV (p = 0.022; HR, 0.53; 95% CI: 031 - 0.91) but not in those with limited disease, stage I, II and IIIa (p = 0.807; HR, 1.11; 95% CI, 0.48).

We analysed the survival of patients in relation to SCLC and NSCLC according to stages.

Our study included 55 patients with SCLC. We compared the survival of patients with SCLC-LD [22], with a group of patients with SCLC-ED [33] from the onset of first symptoms and we got statistically significant difference in survival (p < 0.001). Median survival of the group with SCLC-LD was 48 weeks (95% CI: 22.27 - 73.73), while median survival of the group with SCLC-ED was 30.00 weeks (95% CI: 24.44 - 35.56).

There was statistically significant difference (p < 0.004) in the survival of patients with SCLC from diagnosis, in relation to the stage of disease. Median survival of the patients with limited disease was 40 weeks (95% CI: 29.07 - 50.93), while median survival of the ones with the advanced stage disease was 18 weeks (95% CI: 15.77 - 20.23).

Having analysed the survival of patients with NSCLC from the onset of first symptoms, we concluded that the longest survival was in patients with stage I disease, who were all alive when the study was completed. Median survival was 88.00 weeks in stage II NSCLC patients, 62.00 weeks in stage IIIa patients, 37.00 weeks in stage IIIb patients, and 26.00 weeks in patients with stage IV NSCLC.

There was no significant difference in the survival of patients with stage I and II NSCLC when a delay from the onset of first symptoms was observed. There was a difference in survival of patients with stage I and II disease was compared with those with the advanced stages IIIb and IV, when a delay from the first symptoms was observed.

Having analysed the survival of patients with NSCLC in relation to delay from diagnosis, there was statistically significant difference in the survival of patients with stage I and II and patients with the advanced disease, stage III b and IV. In compliance with the defined objectives, we analysed the survival of patients in relation to metastasis. Metastases were found in 32.5% of the patients. The most frequent localization of metastases was in liver (22.5%). There is a high statistically significant difference in the survival both from the onset of fist symptoms and from diagnosis, in relation to the presence of metastases (p < 0.005).

In the study by Mydral G., *et al.* [2] the survival of the patients with NSCLC was "unexpectedly" shorter in patients with a shorter delay from first symptoms to treatment. In patients who received treatment in less than 3 months the 3 year survival was 11%, while patients for whom there was a delay of more than 6 months had a survival of 35%. Moreover, patients with a short hospital delay (less than 30 days) had a poorer prognosis. Their 3 year survival was 19%, as compared with 43% in those with a doctor's delay of more than 3 months.

In their research, Billing., *et al.* [9] found that delay had no bearing on the survival of patients with pN2, arguing that it could be explained by a long time necessary for different types of NSCLC to double in volume.

In the conclusion of their study, Salomaa E-R., *et al.* [16] say that a longer doctors' delay does not correlate with poor prognosis of patients with advanced stage of NSCLC. Although a delay does not influence better survival rates in patients with limited NSCLC, efficient diagnostics increases the number of resectable tumours and thereby improves the prognosis of these patients.

Lung carcinoma is still a great medical challenge all over the world. In view of the research conducted so far, there are four possible ways to reduce the death rate:

- Prevention (reduction of smoking);
- Early diagnosis by means of new screening technologies;
- Adequate approach to the patients in a more efficient health system;
- Improvement of treatment options.

Fatalistic attitude of doctors towards this disease has changed, and it a lot of effort and funding is now invested in the clinical practice in order to improve the diagnostic procedures for this disease. A part of the efforts focuses on the reduction of a health service delay. Better coordination among doctors and team approach to treatment are the basis for a more efficient treatment of the patients with lung carcinoma. If the time intervals are reduced to minimum, the possibility of early detection of this disease will be higher, as well as the chances to "prolong" the survival of these patients.

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