Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the *Vojnosanitetski Pregled*. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article **EFFECTS OF BIOLOGICAL MARKERS ON OVERALL SURVIVAL IN SURGICALLY TREATED PATIENTS WITH NON SMALL CELL LUNG CANCER**

**UTICAJ BIOLOŠKIH MARKERA NA UKUPNO PREŽIVLJAVANJE OPERISANIH PACIJENATA SA NESITNOĆELIJSKIM KARCINOMOM PLUĆA**

Authors Olivera Lončarević *, Slobodan Lončarević †, Berislav Vekić ‡, Leonida Đukanović §, Jelena Vuković *, Nemanja Rančić ||, Vojnosanitetski pregled (2020); Online First March, 2020.

UDC:

DOI: [https://doi.org/10.2298/VSP191030035L](https://doi.org/10.2298/VSP191030035L)

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appears in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
EFFECTS OF BIOLOGICAL MARKERS ON OVERALL SURVIVAL IN
SURGICALLY TREATED PATIENTS WITH NON SMALL CELL LUNG CANCER

UTICAJ BIOLOŠKIH MARKERA NA UKUPNO PREŽIVLJAVANJE
OPERISANIH PACIJENATA SA NESITNO-ČELIJSKIM KARCINOMOM PLUĆA

Olivera Lončarević *, Slobodan Lončarević †, Berislav Vekić ‡, Leonida Đukanović §,
Jelena Vuković *, Nemanja Rančić ||

*Pulmonology Clinic, Military Medical Academy, Belgrade, Serbia; † Maxillofacial Surgery Clinic, Military Medical Academy, Belgrade, Serbia; ‡ Department of Surgery, Clinical Center Dr Dragiša Mišović; School of Medicine, University of Kragujevac, Kragujevac, Serbia; § BELhospice - Center for Palliative Care and Palliative Medicine, Belgrade; ||Center for Clinical Pharmacology; Institute of Radiology; Medical Faculty Military Medical Academy, University of Defense, Belgrade, Serbia

Correspondence to: Nemanja Rančić, MD, PhD; Military Medical Academy, Belgrade, Serbia; E-mail: nece84@hotmail.com; Tel: +381638524443

Running head: Biomarkers in Non-Small Cell Lung Cancer
Abstract

**Background/Aim.** Non-Small Cell Lung Cancer (NSCLC) is one of the most common malignant tumors and a leading cause of cancer-related deaths. The aim of this study was to evaluate impact of biological markers on the overall survival rate in surgically treated NSCLC patients who received adjuvant chemotherapy and/or radiation therapy. **Methods.** This retrospective case series study was conducted at the Pulmonology Clinic and the Clinic for Chest Surgery, Military Medical Academy, Serbia. Patients with NSCLC were treated in the time period between 2008 and 2017. The survival analysis performed was based on immunohistological findings, histology type and tumor, node, metastasis (TNM) stages. **Results.** The mortality rate was higher in the adenocarcinoma patient group compared to the squamous cell carcinoma group, albeit without statistical significance (58.3% vs. 31.2%, respectively, p=0.175). Overall survival was lower in the adenocarcinoma patient group compared to the squamous cell carcinoma group (by approximately 750 days). Likewise, overall survival was lower in the adenocarcinoma patient group compared to the squamous cell carcinoma group for CD31 positive (p=0.029), p-63 positive (p=0.049), MMP-9 positive (p=0.032) and MMP-2 positive patients (p=0.016). **Conclusion.** Adenocarcinoma is a more aggressive cancer type in comparison to squamous cell carcinoma with a lower overall survival. Our research showed a poorer overall survival in the adenocarcinoma group compared to the squamous cell carcinoma group in CD31, p-63, MMP-9 and MMP-2 positive patients.

**Key words:** Non-Small Cell Lung Cancer; overall survival; biological markers; TNM classification stage; histology type
Apstrakt

**Uvod/Cilj.** Nesitnoćelijski karcinom pluća (NSCLC) je jedan od najčešćih malignih tumora i vodeći je uzrok smrti povezane sa karcinomima. Cilj ove studije je da analizira uticaj bioloških markera na stopu ukupnog preživljavanja u pacijenata sa NSCLC koji su operisani i nakon toga su dobijali adjuvantnu hemioterapiju i/ili radioterapiju. **Metode.** Ovo je retrospektivna studija tipa serije slučajeva u Klinici za pulmologiju i Klinici za grudnu hirurgiju, Vojnomedicinske akademije. Pacijenti sa NSCLC lečeni su tokom perioda od deset godina (2008-2017). Ovo je analiza preživljavanja na osnovu imunohistohemijskih nalaza, patohistološkog tipa i TNM stadijuma. **Rezultati.** Stopa mortaliteta je bila veća u grupi pacijenata sa adenokarcinomom u poređenju sa grupom pacijenata sa skvamocelularnim karcinomom ali razlika nije bila značajna (58,3% vs. 31,2%, p=0,175). Ukupno preživljavanje je bilo manje kod pacijenata sa adenokarcinomom u odnosu na one sa skvamocelularnim karcinomom (oko 750 dana). S druge strane, ukupno preživljavanje je bilo manje kod pacijenata sa adenokarcinomom u poređenju sa skvamocelularnim karcinomom kod CD31 pozitivnih (p=0,029), p-63 pozitivnih (p=0,049), MMP-9 pozitivnih (p=0,032) i MMP-2 pozitivnih pacijenata (p=0,016). **Zaključak.** Adenokarcinom je značajno agresivniji karcinom u poređenju sa skvamocelularnim karcinomom i pokazuje kraće vreme ukupnog preživljavanja. Ukupno preživljavanje je bilo kraće kod pacijenata sa adenokarcinomom u poređenju sa skvamocelularnim karcinomom kod CD31, p-63, MMP-9 i MMP-2 pozitivnih pacijenata.

**Ključne reči:** nesitnoćelijski karcinom pluća; ukupno preživljavanje; biološki markeri; TNM stadijum; patohistološki tip
Introduction

Lung cancer is one of the most common malignant tumors and a leading cause of cancer-related deaths\(^1\). About 80% of all lung cancers are Non-Small Cell Lung Cancer (NSCLC), i.e. squamous cell carcinoma and adenocarcinoma\(^2,\)\(^3\).

The NSCLC significantly decrease overall survival, life quality and working ability of patients, but increase direct and indirect medical cost\(^4\). Treatment options for patients with NSCLC consist of combined surgical treatment, radiation therapy and/or one of the chemotherapy treatment protocols based on the stage of illness, histology type and tumor marker findings and other parameters\(^5\).

Surgery represents a treatment of choice for patients with NSCLC stage I-IIIA according to tumor, node, metastasis (TNM) 8\(^{th}\) edition classification\(^6,\)\(^7,\)\(^8\). In addition to surgery, patients with resected NSCLC stage II-IIIA, who have a high risk of relapse, are treated with adjuvant chemotherapy and/or radiation therapy\(^9\). Patients with stage IIB and IV NSCLC are generally treated with chemotherapy and radiation therapy. For NSCLC stage I and II, radiation therapy alone is considered effective only when surgical resection is not possible either due to limited pulmonary reserve or the presence of comorbidities\(^10\).

Histology and immunohistochemistry (IHC) analysis, as well as specific gene expression assessment, may become a predictive factor for response to chemotherapy in the future clinical research and patient treatment\(^11\). Expression of biomarkers (for example, HER-2, BCL-2, CD-31, p-63, BRAF, KRAS, etc.) can be tested at a protein level using IHC, while mRNA levels can be determined through reverse transcriptase PCR (RT-PCR)-based assays. Therefore, these biomarkers are currently not in use in daily practice. Many biomarkers in lung cancer were point mutations and rearrangements in specific genes including EGFR, anaplastic lymphoma kinase, HER-2, BCL-2, CD-31, p-63, MMPs, BRAF, NUT, MET, ROS1, DDR2, FGFR1, KRAS, and PTEN\(^11\). These biomarkers might potentially provide additional information for clinical decision making.

The overall five-year survival rate for all lung cancer in stage with localized disease is about 52.2%, in stage with regional metastatic disease 25%, and in stage with distant metastatic disease 4%\(^12\).
The aim of this study is to evaluate impact of biological markers on the overall survival rate in surgically treated NSCLC patients, and after the adjuvant chemotherapy and/or radiation therapy.

Methods

Patient’s data

This retrospective case series study of patients with NSCLC was designed as survival analysis based on immunohistological findings, histology type and TNM stages. Forty (40) NSCLC patients (17 females and 23 males; average age 59.22±8.31 years) were treated at the Pulmonology Clinic and Chest Surgery Clinic of the Military Medical Academy in Serbia, and were followed up over the period between 2008 and 2017.

Clinical files from all patients with clinically confirmed lung cancer admitted between 2010 and 2015 to the institutional healthcare network of the Military Medical Academy were accessed in both hard and electronic copies from the hospital registries. The following data were analyzed: demographic characteristics (age, gender), overall survival rate, immunohistological findings, histology type and TNM stages of NSCLC.

TNM Stage and Patients Treatment

A first step done in our hospital was to classify patients with NSCLC according to the TNM stages. T1N0M0 was classified as stage IA; T2N0M0 as stage IB; T1N1M0 as stage IIA; T2N1M0 and T3N0M0 as stage IIB; and T3N1M0, T1N2M0, T2N2M0, T3N2M0 as stage IIIA. Stage IIIB was classified as T4 any N M0 and any T N3M0, whereas stage IV was classified as any T any N M1.

A second step consisted of treating patients with NSCLC, according to their TNM stages. TNM stage I patients were treated only surgically. TNM stage IIA to IIIA patients were treated surgically and with adjuvant chemotherapy (etoposide and cisplatin -- EP/PE protocol) and/or radiation therapy.

The above chemotherapy protocol was applied as follows: cisplatin at 60 mg/m² IV administered on day 1, plus etoposide at 120 mg/m² IV administered on days 1, 2 and 3, every 21 days for 4 cycles. Alternatively, cisplatin at 80 mg/m² IV was administered on day 1, plus etoposide at 100 mg/m² IV on days 1, 2 and 3, every 28 days for 4 cycles.
Radiotherapy was applied in patients with positive resection surface for malignancy and with N2 TNM stage.

Histology and IHC

Following tumor excision, collected tissue was formalin-fixed and paraffin embedded (FFPE) as described below. Tissue slides were morphologically diagnosed at the Institute for Pathology and Forensic Medicine, and subsequently tested for a series of biomarkers using IHC standard protocol developed at the Laboratory for Immunohistochemistry and Electron Microscopy of the Institute for Medical Research.

Excised tissue was fixed in 5% neutral-buffered formalin, and processed in V.I.P. Sakura apparatus for automatic fixation, dehydration and paraffin embedding. Tissue blocks were cut at 5-7 µm, and sections mounted on separate adherent chips (Super-Frost), and then dried at 56°C for one hour prior to staining.

Antibodies for immunostaining were applied according to manufacturers’ recommendations. The following primary antibodies were used for IHC: HER-2, BCL-2, CD-31, p-63, MMP-2, MMP-9, and MMP-14.

Statistical Analyses

Continuous variables were presented as median with inter quartile range (IQR). Categorical variables were reported as frequencies. Differences between categorical variables were tested by Chi-square test, while significance of difference between continuous variables was tested by non-parametric Mann-Whitney U test. Overall survival estimates were calculated using the Kaplan-Meier method [mean (95% confidence interval - CI 95%)], and Log-rank (Mantel-Cox) test to assess differences between groups of NSCLC. A p-value of less than 0.05 was considered statistically significant.

Ethics Committee Approval

The study was conducted in accordance to the Declaration of Helsinki, and the protocol reviewed and approved on September 6, 2015 by the regional Ethics Committee of the Military Medical Academy.

Results
In our study, we analyzed 40 patients with NSCLC (16 patients with squamous cell carcinoma and 24 with adenocarcinoma). Females were frequently in the adenocarcinoma group (13 or 54.2% out of 24 patients), while males were frequently in the squamous cell carcinoma group with (12 or 75.0% out of 16 patients) (Chi-square test; p=0.133). Differences according to age were not shown between groups [median age 61.04 (IQR 52.90-65.64) in patients with squamous cell carcinoma; median age 58.57 (IQR 54.16-66.09) in adenocarcinoma; Mann-Whitney test; p=0.924].

Overall survival for all patients followed according to biomarker type was not statistically different (Log Rank (Mantel-Cox) test; p>0.05) (Table 1).

The mortality rate was higher in the group of patients with adenocarcinoma compared to the squamous cell carcinoma patient group (58.3% or 14 out of 24 patients, and 31.2% or 5 out of 16 patients respectively). However, it is to note that this difference did not show significant (Chi-square test; p=0.175).

Overall survival of patients according to histology type of NSCLC (adenocarcinoma vs. squamous cell carcinoma) was not statistically different (Log Rank (Mantel-Cox) test; p=0.057) (Figure 1). However, cumulative survival was lower by approximately 750 days in the patient group with adenocarcinoma in comparison to group with squamous cell carcinoma (estimated mean of 817.0 (561.2-1,072.7) vs. 1,566.4 (1,149.4-1,983.4) days respectively with 95% confidence interval).

Overall survival of patients with adenocarcinoma and squamous cell carcinoma according to interval from surgery/ surgical resection to recurrence was presented in Table 2. Statistically significant difference was not observed between the groups. Cumulative survival was lower in the patient recurrence group with adenocarcinoma in comparison to the group with squamous cell carcinoma by approximately 810 days (Figure 2).

Overall survival was estimated and compared among patients according to preoperative TNM stage in both patient groups (Table 3). There was no statistically significant difference in survival between patients in stages I, II and IIIA within the adenocarcinoma (p=0.060) and the squamous cell carcinoma group (p=0.970). However, overall survival between adenocarcinoma and squamous cell carcinoma according to initial TNM stage showed that patients with adenocarcinoma had lower statistically significant survival rate compared to the patients with squamous cell carcinoma in TNM stage IIIA (Log
Rank (Mantel-Cox) test; p=0.007) (mean 374.4 days vs. 1586.4 days, respectively) (Figure 3).

No significant differences were observed between adenocarcinoma and squamous cell carcinoma by distribution of patients according to biological markers (Table 4). The patients were most frequently positive for BCL-2, CD-31, p-63, MMP-9 and MMP-2, but rarely for HER-2 and MMP-14.

Overall survival was estimated and compared among NSCLC patients according to status of biological markers in two patient groups studied (Table 4). There was no statistically significant difference in survival between patients with positive and negative biological markers regardless of NSCLC type. Nonetheless, cumulative survival was lower in the adenocarcinoma patient group compared to the squamous cell carcinoma group for CD31 positive (Log Rank (Mantel-Cox) test p=0.029) (Figure 4), p-63 positive (p=0.049) (Figure 5), MMP-9 positive (p=0.032) (Figure 6) and MMP-2 positive patients (p=0.016) (Figure 7).

**Discussion**

Non-small cell lung cancer is one of the major causes of cancer-related deaths. To analyze survival in our NSCLC patients, we conducted a retrospective case-series study using the follow-up data from a time period between 2008 and 2017. Our study design aimed at assessing the overall survival in NSCLC patients according to specific biomarkers expression, TNM stage and histology type.

In the operable NSCLC patients, adjuvant chemotherapy has been considered a standard modality of treatment following surgical resection of the tumor. Besides, molecularly targeted therapy has significantly improved outcomes of patients with metastatic form of NSCLC. Nevertheless, for the majority of patients, platinum-based chemotherapy remains the gold standard treatment, and has led to significantly improved survival outcomes with approximately 10-11 months median survival.

In our study, there were more male patients in the squamous cell carcinoma group, while female patients dominated the adenocarcinoma group. Men develop tracheal, bronchus and lung cancer more often compared to women (1/18 for men; 1/45 for women). The estimated numbers of lung cancer cases worldwide has increased by 44% in men and 76% in women since 1985. The higher rate increase in women has been attributed to the fact that
cigarette smoking in female population peaked two decades later than in male. Our squamous cell carcinoma patients were not significantly older compared to the adenocarcinoma group (median age 61.04 vs. 58.57, respectively). Comparably, in another study, squamous cell carcinoma patients were slightly older when compared to adenocarcinoma patients (median age 69 vs. 65, respectively).

Patients with adenocarcinoma had poorer prognosis compared to squamous cell carcinoma patients. Similarly, in our study, the mortality rate was significantly higher in the adenocarcinoma group (58.3%) as opposed to squamous cell carcinoma group (31.2%). According to the literature, generally, the five-year survival rate for all NSCLC patients in stage IA, IB, IIA and IIB is about 49%, 45%, 30% and 31% respectively. This rate for NSCLC patients in stage IIIA and IIIB is about 14%, 5%, respectively.

Overall survival of patients according to recurrence is of major significance. Recurrence rates reported following surgical cancer resection range from 30% to 75%. The majority of recurrent tumors are distant, and more than 80% of recurrences occur within the first two years after resection. Cumulative survival was lower in our patient recurrence group with adenocarcinoma compared to the squamous cell carcinoma group by about 810 days. This is in line with our findings showing adenocarcinoma as a more aggressive cancer type than squamous cell carcinoma.

The complete resection of early stage NSCLC offers to patients high hopes for a successful therapeutic outcome. However, the recurrence rates post-resection remain high. For that reason, right from the beginning of therapy in NSCLC patients, a complete surgical removal needs to be ensured both macroscopically and microscopically. Often, occult micrometastatic cancer cells, already present systemically at the time of surgery, remain undetected by standard staging methods suggesting an underestimation of the true tumor stage. Else, dissemination of cancer cells might occur during the handling of the tumor during surgery.

Overall survival according to TNM stages was observed between patients with adenocarcinoma, as well as squamous cell carcinoma. Statistical significance was not observed between our patients vs. squamous cell carcinoma in TNM stage groups IA, IB, IIA and IIB, but this difference was shown between the groups in IIIA stage. Overall survival was lower among stage IIIA adenocarcinoma patients compared to squamous cell carcinoma patients of the same stage (mean 374.4 days vs. 1586.4 days, respectively). This evidence is
also in line with adenocarcinoma being more aggressive cancer type when compared to squamous cell carcinoma.

After curative resections, patients with lung cancer at the same TNM stage show wide variations in their recurrence onset and overall survival. The current TNM staging system, which is based on clinical and pathological findings, may have achieved the limit of its relevance. Being able to predict the exact likelihood and timing of relapse can help guide the administration of adjuvant therapies. There are two methods for identifying factors related to recurrence and low overall survival following surgery: expression of tumor markers and molecular biological techniques. Excellent prognostic markers for prediction the postoperative recurrence of cancer are KRAS, Ki-67, p16, EGFR, and others. Since histological differentiation, vessel invasion, lymphatic permeation and pleural invasion have been reported poor prognostic factors for the disease free survival, an extensive pathological investigation is also of high significance.

Personalized medicine by targeting appropriate molecular targets in tumors has helped improve survival in NSCLC patients. Matrix metalloproteinases (MMPs) and zinc-dependent endopeptidases play roles within various areas of cancer pathology. Tumor growth, metastasis, angiogenesis, and MMP activation is increased in nearly all human cancers when compared to normal tissue. MMPs are involved in the degradation of extracellular matrix. In addition, MMPs are known to influence lung cancer metastatic properties, and are involved several signaling pathways (ECM, collagen, regulates polarization of Th1/Th2 inflammatory response; Springolipid and Ephrin receptor-signaling pathway (ET-1); N-cadherin, N-cadherin, VSMC-ECM attachment; IGF-2, VEGF-B and VEGF-Dsignaling pathways; p38, JNK and NF-κB pathways). Overall, increased levels of specific MMPs have been associated with NSCLC progression.

MMP-14 is a critical protein in cancer invasion and metastasis. Invasion through collagen networks and subsequent collagenolysis relies principally on MMP-14 and not on secreted MMPs. MMP-14 expression has been correlated with primary tumor growth and metastasis as well as angiogenesis. Detailed analysis of MMP-14-promoted tumor growth has suggested that a cytoplasmic domain is required for the MMP-14 enhanced tumor growth.

MMP-2 has a role in extracellular matrix disassembly, increased cell proliferation, invasion/migration and angiogenesis. Strong immunohistochemical staining for MMP-2 in
tumor tissue predicts poor survival in lung cancer patients. MMP-2 has been implicated in lymphatic and vascular invasion of NSCLC, thus prognostic value of MMP-2 expression in NSCLC is of great significance. MMP-2 overexpression predicts a poor prognosis in early-stage NSCLC. This study shows that MMP-2 overexpression correlates with early cancer-related death. Other MMP subclasses are also associated with a degree of lung cancer aggressiveness. It is of note, that one systematic review suggests that MMP-2 expression has a poor prognostic significance of NSCLC patient’s survival.

MMP-9 has a role in extracellular matrix remodeling, increased cell proliferation, invasion/migration and angiogenesis. Highly expressed MMP-9 correlates with shortened survival of NSCLC patients. MMP-9 expression is an independent prognostic marker for resected stage NSCLC. Thus, MMP-9 is a novel biomarker significantly and independently predicting worse prognosis of resected stage NSCLC. In a different study, tumor MMP-9 expression was associated with poor outcomes in adenocarcinoma, but not in squamous cell carcinoma patients. MMP-9 expression was identified as an independent marker of relapse in completely resected lung adenocarcinoma.

In NSCLC patients, genetic aberrations of human epidermal growth factor-2 (HER-2) signaling pathway are associated with different sensitivity to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). This is a plausible mechanism and prognostic role of acquired resistance to the EGFR TKIs in EGFR-mutated tumors. Although in our study a vast majority of patients in both cancer groups were HER-2 negative, our positive adenocarcinoma patients showed lower survival rate compared to HER-2 negative adenocarcinoma patients. Gene amplification is a well-known mechanism of proto-oncogene activation and has been described in many human malignancies, including lung tumors. However, HER-2 amplification seems far less common in NSCLC compared to other cancers. Recently, the predictive role of HER-2 overexpression has been more extensively studied with a purpose to identify anti-HER-2 agents applicable in NSCLC patients.

BCL-2 overexpression is associated with better outcome and survival of the patients with NSCLC. Patients with positive BCL-2 expression have a better survival rate compared to patients with negative BCL-2 expression. Our study showed comparable findings.

The intensity of neoangiogenesis in a tumor can be reliably evaluated by measuring the intratumoral microvessel density of CD-31 cell membrane protein. CD-31 is an integral
endothelial membrane protein, that mediates cell-to-cell adhesion. Statistics has shown a more significant survival rate in NSCLC patients with high CD-31 expression compared to patients with lower CD-31 expression.

Expression of p-63, an established marker of squamous differentiation, is also present in NSCLC patients. P-63 is a transcription factor that transactivates p-53 target genes and induces apoptosis when expressed in cells. The p-63 gene amplification and overexpression may have important implications in tumorigenesis. In our previous study, patients with weak p-63 expression had a significantly shorter overall survival than patients with no p-63 expression, and a tendency of shorter overall survival than patients with p-63 expression. Patients with negative p-63 expression have a tendency to worse prognosis compared to patients with p-63 expression. On the other hand, in study done by Ko et al., negative expression of p-63 was associated with a short recurrence interval of the disease and shorter survival in NSCLC.

Based on our results of our study, tumor (biological) markers represent significant negative prognostic indicators in all patients with NSCLC regardless of the histological tumor subtype. All patients with positive marker expression had a short recurrence interval of the disease, as well as a short overall survival. These data should be considered when deciding on patient treatment following surgical resections. We propose that patients with positive expression of BCL-2, CD-31, p-63, MMP-9, MMP-2, HER-2 and MMP-14 should receive adjuvant chemotherapy irrespective of their TNM clinical stage and tumor histological type.

**Limitation of the study:** Our study is limited by a low size effect and a retrospective character; the optimal management of lung cancer patients according to biomarkers needs to be determined by prospective clinical trials in large patient cohorts.

**Conclusion**

In conclusion, adenocarcinoma is more aggressive compared to squamous cell carcinoma showing a lower overall survival in patients. Cumulative survival was lower by approximately 750 days in adenocarcinoma patients in comparison with squamous cell carcinoma patients. In addition, cumulative survival was lower in adenocarcinoma patient
group in comparison with squamous cell carcinoma group in CD31, p-63, MMP-9 and MMP-2 positive patients. Therefore, these biological markers have a significant prognostic value for NSCLC patient survival. Biological marker expression may be a useful clinical prognostic tool of therapeutic outcome.

References

1. Cancer.org/ [homepage on the Internet]. American Cancer Society. Cancer facts and figures 2016. [cited 2019 June 13]. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf

2. Fenchel K, Sellmann L, Dempke WC. Overall survival in non-small cell lung cancer-what is clinically meaningful? Transl Lung Cancer Res. 2016;5(1):115-9.

3. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.

4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008;58(2):71-96.

5. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, editors. World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004.

6. Zdravlje.gov.rs [homepage on the Internet]. Milašinović G, editor. Nationality guidelines of good clinical practice: lung cancer [Serbian]. Belgrade: National Expert Commission for the development and implementation of good clinical practice guide; 2012. [cited 2019 June 13]. Available from: http://www.zdravlje.gov.rs/downloads/2011/Decembar/Vodici/Vodic%20za%20dijagnostikovanje%20i%20lecenje%20karcinoma%20pluca.pdf

7. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584-94.
8. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. Quant Imaging Med Surg. 2018;8(7):709-18.

9. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350(4):351-60.

10. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. Thorax. 2001;56(8):628-38.

11. Thunnissen E, van der Oord K, den Bakker M. Prognostic and predictive biomarkers in lung cancer. A review. Virchows Arch. 2014;464(3):347-58.

12. Seer.cancer.gov [homepage on the Internet]. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al, editors. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, MD: National Cancer Institute. [cited 2019 June 13]. Available from: http://seer.cancer.gov/csr/1975_2009_pops09/

13. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest. 1997;111(6):1710-7.

14. Durm G, Hanna N. Second-Line Chemotherapy and Beyond for Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017;31(1):71-81.

15. Heist RS. First-Line Systemic Therapy for Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017;31(1):59-70.

16. Tam K, Daly M, Kelly K. Treatment of Locally Advanced Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017;31(1):45-57.

17. Chuang JC, Liang Y, Wakelee HA. Neoadjuvant and Adjuvant Therapy for Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017;31(1):31-44.

18. Park SJ, More S, Murtuza A, Woodward BD, Husain H. New Targets in Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017;31(1):113-29.

19. Crinò L, Weder W, van Meerbeeck J, Felip E; ESMO Guidelines Working Group. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v103-15.
20. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346(2):92-8.

21. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61(4):212-36.

22. Kawase A, Yoshida J, Ishii G, Nakao M, Aokage K, Hishida T, et al. Differences between squamous cell carcinoma and adenocarcinoma of the lung: are adenocarcinoma and squamous cell carcinoma prognostically equal? Jpn J Clin Oncol. 2012;42(3):189-95.

23. Lončarević O, Aćimović S, Vuković J, Stojisavljević M, Marić N, Lončarević S, et al. Overall survival of patients with non-small cell lung cancer after surgery treatment. Vojnosanit Pregl. 2018;75(12):1157-64.

24. Kawase A, Yoshida J, Ishii G, Nakao M, Aokage K, Hishida T, et al. Differences between squamous cell carcinoma and adenocarcinoma of the lung: are adenocarcinoma and squamous cell carcinoma prognostically equal? Jpn J Clin Oncol. 2012;42(3):189-95.

25. Cancer.org/ [homepage on the Internet]. American cancer society. Non-small cell lung cancer stages. [last revised: 2016 May 16, cited 2019 June 13]. Available from: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates

26. Sasaki H, Suzuki A, Tatematsu T, Shitara M, Hikosaki Y, Okuda K, et al. Prognosis of recurrent non-small cell lung cancer following complete resection. Med Lett. 2014;7(4):1300-4.

27. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res. 2014;3(4):242-9.

28. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Risk factors for tumor recurrence in patients with early-stage (stage I and II) non-small cell lung cancer: patient selection criteria for adjuvant chemotherapy according to the seventh edition TNM classification. Chest. 2011;140(6):1494-502.
29. Shoji F, Haro A, Yoshida T, Ito K, Morodomi Y, Yano T, et al. Prognostic significance of intratumoral blood vessel invasion in pathologic stage IA non-small cell lung cancer. Ann Thorac Surg. 2010;89(3):864-9.

30. Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol. 2014;25(9):1681-90.

31. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Transl Lung Cancer Res. 2016;5(3):288-300.

32. Zarrabi K, Dufour A, Li J, Kuscu C, Pulkoski-Gross A, Zhi J, et al. Inhibition of matrix metalloproteinase 14 (MMP-14)-mediated cancer cell migration. J Biol Chem. 2011;286(38):33167-77.

33. Guo CB, Wang S, Deng C, Zhang DL, Wang FL, Jin XQ. Relationship between matrix metalloproteinase 2 and lung cancer progression. Mol Diagn Ther. 2007;11(3):183-92.

34. Merchant N, Nagaraju GP, Rajitha B, Lammata S, Jella KK, Buchwald ZS, et al. Matrix metalloproteinases: their functional role in lung cancer. Carcinogenesis. 2017;38(8):766-80.

35. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell. 2010;141(1):52-67.

36. Passlick B, Sienel W, Seen-Hibler R, Wöckel W, Thetter O, Mutschler W, et al. Overexpression of matrix metalloproteinase 2 predicts unfavorable outcome in early-stage non-small cell lung cancer. Clin Cancer Res. 2000;6(10):3944-8.

37. Qian Q, Wang Q, Zhan P, Peng L, Wei SZ, Shi Y, et al. The role of matrix metalloproteinase 2 on the survival of patients with non-small cell lung cancer: a systematic review with meta-analysis. Cancer Invest. 2010;28(6):661-9.

38. Li XX, Li RJ, Zhao LJ, Liu NB, Wang P. Expression of molecular factors correlated with metastasis in small cell lung cancer and their significance. Int J Clin Exp Pathol. 2015;8(11):14676-84.

39. Zhang J, Qi J, Chen N, Fu W, Zhou B, He A. High expression of a disintegrin and metalloproteinase-9 predicts a shortened survival time in completely resected stage I non-small cell lung cancer. Oncol Lett. 2013;5(5):1461-1466.
40. Lee CY, Shim HS, Lee S, Lee JG, Kim DJ, Chung KY. Prognostic effect of matrix metalloproteinase-9 in patients with resected Non small cell lung cancer. J Cardiothorac Surg. 2015;10:44.

41. Ricciardi GR, Russo A, Franchina T, Ferraro G, Zanghì M, Picone A, et al. NSCLC and HER2: between lights and shadows. J Thorac Oncol. 2014;9(12):1750-62.

42. Mazières J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013;31(16):1997-2003.

43. Zhao XD, He YY, Gao J, Zhao C, Zhang LL, Tian JY, et al. High expression of Bcl-2 protein predicts favorable outcome in non-small cell lung cancer: evidence from a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2014;15(20):8861-9.

44. Tomita M, Matsuzaki Y, Edagawa M, Shimizu T, Hara M, Onitsuka T. Prognostic significance of bcl-2 expression in resected pN2 non-small cell lung cancer. Eur J Surg Oncol. 2003;29(8):654-7.

45. Mineo TC, Ambrogi V, Baldi A, Rabitti C, Bollerò P, Vincenzi B, et al. Prognostic impact of VEGF, CD31, CD34, and CD105 expression and tumour vessel invasion after radical surgery for IB-IIA non-small cell lung cancer. J Clin Pathol. 2004;57(6):591-7.

46. Conde E, Angulo B, Redondo P, Toldos O, García-García E, Suárez-Gauthier A, et al. The use of P63 immunohistochemistry for the identification of squamous cell carcinoma of the lung. PLoS One. 2010;5(8):e12209.

47. Conde E, Angulo B, Redondo P, Toldos O, Garcia-Garcia E, Suarez-Gauthier A, et al. The use of p63 immunohistochemistry for the identification of squamous cell carcinoma of the lung. PLoS One. 2010;5(8):e12209.

48. Massion PP, Taflan PM, Jamshedur Rahman SM, Yildiz P, Shyr Y, Edgerton ME, et al. Significance of p63 amplification and overexpression in lung cancer development and prognosis. Cancer Res. 2003;63(21):7113-21.

49. Cvetković G, Plavec G, Tatamirović Ž, Jović M, Lončarević O, Trifunović Z, et al. Expression of P63 as predictive and prognostic factor in advanced non-small-cell lung cancer. Vojnosanit Pregl. 2018;75(4):366-73.
50. Ko E, Lee BB, Kim Y, Lee EJ, Cho EY, Han J, et al. Association of RASSF1A and p63 with poor recurrence-free survival in node-negative stage I-II non-small cell lung cancer. Clin Cancer Res. 2013;19(5):1204-12.
Table 1

Overall survival in all patients with Lung Cancer according to biological markers tested (censored – alive at the end of the follow-up period)

| Marker tested | Total number | Number of death events (%) | Censored Number (%) | Survival (days) – estimated mean (CI 95%) | p value |
|---------------|--------------|----------------------------|---------------------|------------------------------------------|---------|
| HER-2 negative | 32           | 14                         | 18 (55.2)           | 1262.8 (929.7-1596.0)                    | p=0.316* |
| HER-2 positive | 8            | 5                          | 3 (37.5)            | 655.0 (354.2-955.8)                      |         |
| BCL-2 negative | 1            | 1                          | -                   | 540.0 (540.0-540.0)                      | p=0.447* |
| BCL-2 positive | 39           | 18                         | 21 (53.8)           | 1230.9 (928.8-1533.1)                    |         |
| CD31 negative  | 5            | 2                          | 3 (60.0)            | 766.8 (506.1-1027.5)                     | p=0.728* |
| CD31 positive  | 35           | 17                         | 18 (51.4)           | 1194.4 (881.4-1507.4)                    |         |
| p-63 negative  | 2            | 1                          | 1 (50.0)            | 756.5 (456.4-1056.5)                     | p=0.875* |
| p-63 positive  | 38           | 18                         | 20 (52.6)           | 1206.6 (901.6-1511.5)                    |         |
| MMP-9 negative | 7            | 4                          | 3 (42.9)            | 720.6 (533.6-907.5)                      | p=0.829* |
| MMP-9 positive | 33           | 15                         | 8 (54.5)            | 1240.9 (911.8-1570.0)                    |         |
| MMP-2 negative | 19           | 7                          | 12 (63.2)           | 1113.6 (817.0-1410.2)                    | p=0.303* |
| MMP-2 positive | 21           | 12                         | 9 (42.9)            | 1017.7 (625.4-1410.0)                    |         |
| MMP-14 negative | 33          | 15                         | 18 (54.5)           | 1243.7 (919.4-1568.0)                    | p=0.594* |
| MMP-14 positive | 7            | 4                          | 3 (42.9)            | 663.3 (329.6-923.3)                      |         |

*- Log Rank (Mantel-Cox) test
Figure 1
Kaplan-Meier analysis – survival curves of patients according to histology type of Non-Small Cell Lung Cancer (NSCLC) (censored – alive at the end of the follow-up period)
Table 2

Distribution of overall survival of patients with Non-Small Cell Lung Cancer (NSCLC) according to interval from surgery/ surgical resection to recurrence

| Type of NSCLC          | Recurrence | Total number | Number of death events (%) | Censored Number (%) | Survival (days) – estimated mean (CI 95%) | p value |
|-----------------------|------------|--------------|----------------------------|---------------------|------------------------------------------|---------|
| Adenocarcinoma        | Yes        | 17           | 11 (64.7)                  | 6 (35.3)            | 803.4 (521.7-1,085.1)                     | p=0.940*|
|                       | No         | 7            | 3 (42.9)                   | 4 (57.1)            | 616.7 (328.4-904.9)                       |         |
| Squamous cell carcinoma| Yes       | 6            | 2 (32.3)                   | 4 (66.7)            | 1,615.8 (995.1-2,236.3)                   | p=0.814*|
|                       | No         | 10           | 3 (30.0)                   | 7 (70.0)            | 949.0 (707.0-1,191.0)                     |         |

*- Log Rank (Mantel-Cox) test; Yes Adenocarcinoma / Yes Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.147; No Adenocarcinoma / No Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.316
Figure 2

Kaplan-Meier analysis – survival curves in the patients with recurrence according to histology type of Non-Small Cell Lung Cancer (NSCLC) (censored – alive at the end of the follow-up period)
Table 3

Distribution of overall survival in patients with Non-Small Cell Lung Cancer (NSCLC) according to clinically initially Tumor, Node, Metastasis (TNM) stage

| Type of NSCLC          | TNM stage | Total number | Number of death events (%) | Censored Number (%) | Survival (days) – estimated mean (CI 95%) | P value |
|------------------------|-----------|--------------|-----------------------------|---------------------|------------------------------------------|---------|
| Adenocarcinoma         | IA,IB     | 6            | 3 (50.0)                    | 3 (50.0)            | 1101.5 (708.8-1494.2)                    | p=0.060*|
|                        | IIA,IIIB  | 12           | 6 (50.0)                    | 6 (50.0)            | 810.4 (508.9-1112.0)                     |         |
|                        | IIIA      | 6            | 5 (83.3)                    | 1 (16.7)            | 374.4 (186.6-562.2)                      |         |
| Squamous cell carcinoma| IA,IB     | -            | -                           | -                   | -                                        | p=0.970*|
|                        | IIA,IIIB  | 9            | 3 (33.3)                    | 6 (66.7)            | 971.0 (702.1-1239.9)                     |         |
|                        | IIIA      | 7            | 2 (28.6)                    | 5 (71.4)            | 1586.4 (325.6-947.9)                     |         |

* Log Rank (Mantel-Cox) test; IIA,IIIB Adenocarcinoma / IIA,IIIB Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.380; IIIA Adenocarcinoma / IIIA Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.007
Figure 3

Kaplan-Meier analysis – survival curves in the patients with Non-Small Cell Lung Cancer (NSCLC) in IIIA TNM stage according to histology type (censored - alive at the end of the follow-up period)
Table 4
Overall survival in the patients with Non-Small Cell Lung Cancer (NSCLC) according to biological markers (censored – alive at the end of the follow-up period)

| Type of NSCLC          | Marker tested | Total number | p value | Number of death events (%) | Censored Survival (days) – estimated mean (CI 95%) | p value |
|------------------------|---------------|--------------|---------|-----------------------------|---------------------------------------------------|---------|
| Adenocarcinoma         | HER-2 negative | 18 (75.0%)   | 0.572   | 9 (50.0)                    | 922.8 (621.3 - 1224.2)                              | 0.103   |
|                        | HER-2 positive | 6 (25.0%)    | #       | 5 (83.3)                    | 398.0 (241.9 - 554.1)                                | *       |
| Squamous cell carcinoma| HER-2 negative | 14 (87.5%)   | #       | 5 (35.7)                    | All censored patients in HER-2 positive group       | 0.307   |
|                        | HER-2 positive | 2 (12.5%)    | #       | -                           | 833.0 (566.8 - 1099.2)                               | *       |
| Adenocarcinoma         | BCL-2 negative | 1 (4.2%)     | 1.000   | 1 (100.0)                   | 540.0 (540.0 - 540.0)                                | 0.735   |
|                        | BCL-2 positive | 23 (95.8%)   | #       | 13 (56.5)                   | 833.0 (566.8 - 1099.2)                               |         |
| Squamous cell carcinoma| BCL-2 negative | -            | -       | -                           | -                                                  |         |
| Tumor Type               | Markers         | Positive Cases | Negative Cases | Count (Percentage) | Median (Min - Max) |
|-------------------------|-----------------|----------------|----------------|-------------------|-------------------|
| Adenocarcinoma          | BCL-2 positive  | 16 (100.0%)    | 2 (8.3%)       | 5 (31.2)          | 1566.4 (1149.4 - 1983.4) |
|                         | CD31 negative   | 3 (12.5%)      | 2 (8.3%)       | 1 (33.3)          | 847.3 (601.4 - 1093.2) |
|                         | CD31 positive   | 21 (87.5%)     | 21 (87.5%)     | 13 (61.9)         | 772.1 (504.6 - 1039.5) |
| Squamous cell carcinoma | CD31 negative   | 2 (12.5%)      | 2 (8.3%)       | 1 (50.0)          | 572.5 (182.4 - 962.6)  |
|                         | CD31 positive   | 14 (87.5%)     | 22 (91.7%)     | 4 (28.6)          | 1624.5 (1197.6 - 2051.5) |
| Adenocarcinoma          | p-63 negative   | 2 (8.3%)       | 2 (8.3%)       | 1 (50.0)          | 756.5 (456.4 - 1056.5)  |
|                         | p-63 positive   | 22 (91.7%)     | 22 (91.7%)     | 13 (59.1)         | 799.4 (531.8 - 1067.0)  |
| Squamous cell carcinoma | p-63 negative   | -              | -              | -                 | -                 |
|                         | p-63 positive   | 16 (100.0%)    | 16 (100.0%)    | 5 (31.2)          | 1566.4 (1149.4 - 1983.4) |
| Adenocarcinoma          | MMP-9 negative  | 4 (16.7%)      | 4 (16.7%)      | 2 (50.0)          | 749.7 (530.8 - 968.7)   |

*p = 0.001

**Note:**
- The table represents the percentage and median values for BCL-2, CD31, and MMP-9 expression in adenocarcinoma and squamous cell carcinoma tissues.
- The p-values indicate statistical significance of the differences in expression levels.
|                     | MMP-9 positive | MMP-9 negative | MMP-2 positive | MMP-2 negative | MMP-14 positive | MMP-14 negative | p       |
|---------------------|----------------|---------------|----------------|----------------|----------------|-----------------|---------|
| Squamous cell carcinoma | 20 (83.3%)     | 3 (18.8%)     | 13 (81.2%)      | 3 (23.1%)      | 15 (62.5%)     | 6 (37.5%)       | p=0.215 |
| Adenocarcinoma      | 12 (60.0%)     | 2 (66.7%)     | 3 (33.3%)       | 4 (26.7%)      | 10 (55.6%)     | 8 (44.4%)       | p=0.219 |
|                     | 8 (40.0%)      | 1 (33.3%)     | 6 (66.7%)       | 5 (83.3%)      | 8 (44.4%)      |                 |         |
|                     | 785.7 (505.5 - 1065.9) | 681.7 (239.6 - 1123.7) | 1152.2 (725.0 - 1580.0) | 609.7 (384.7 - 834.7) | 1882.4 (1416.8 - 2348.0) |                 | p=0.141 |
| Adenocarcinoma      | 6 (16.7%)      | 4 (66.7%)     | 2 (33.3%)       | 4 (66.7%)      | 6 (37.5%)      |                 |         |
| Squamous cell carcinoma | 5 (33.3%)      | 10 (66.7%)    |                 |               |                |                 |         |
|                     |                |               |                |               |                | All censored patients in MMP-14 | p=0.494 |
|                     |                |               |                |               |                |                 |         |
|            | MMP-14  | 1 (6.2%) | - | 1 (100.0) | 14 positive group |
|------------|---------|----------|---|-----------|------------------|

#- Chi-square test; *- Log Rank (Mantel-Cox) test; HER-2 positive Adenocarcinoma / HER-2 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.092; HER-2 negative Adenocarcinoma / HER-2 negative Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.330; BCL-2 positive Adenocarcinoma / BCL-2 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.072; CD31 positive Adenocarcinoma / CD31 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.029; p-63 positive Adenocarcinoma / p-63 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.049; MMP-9 positive Adenocarcinoma / MMP-9 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.032; MMP-9 negative Adenocarcinoma / MMP-9 negative Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.730; MMP-2 positive Adenocarcinoma / MMP-2 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.016; MMP-2 negative Adenocarcinoma / MMP-2 negative Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.837; MMP-14 positive Adenocarcinoma / MMP-14 positive Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.330; MMP-14 negative Adenocarcinoma / MMP-14 negative Squamous cell carcinoma Log Rank (Mantel-Cox) test p=0.130
Figure 4
Kaplan-Meier analysis – survival curves in positive CD-31 patients with Non-Small Cell Lung Cancer (NSCLC) according to histology type (censored - alive at the end of the follow-up period)
Kaplan-Meier analysis – survival curves in positive p-63 patients with Non-Small Cell Lung Cancer (NSCLC) according to histology type (censored - alive at the end of the follow-up period)
Figure 6
Kaplan-Meier analysis – survival curves in positive MMP-9 patients with Non-Small Cell Lung Cancer (NSCLC) according to histology type (censored - alive at the end of the follow-up period)
Figure 7
Kaplan-Meier analysis – survival curves in positive MMP-2 patients with Non-Small Cell Lung Cancer (NSCLC) according to histology type (censored - alive at the end of the follow-up period)