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# PROGNOSTIC FACTORS IN NON-SMALL CELL LUNG CARCINOMA

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**Summary**

In recent years, a group of new prognostic factors have been added to the list of well-known clinical prognostic factors of non-small cell lung cancer (NSCLC). Among these are: mutation in K-*ras* oncogene, abnormal p53 proteins as result mutations on p53 tumor suppressor gene, the presence of N-CAM expression as measured by Mab immunostaining, elevated serum levels of neuron specific enolase (NSE) etc.

Today in B&H, these biomarkers not yet fine their place in every day clinical praxis. That is reason why we cannot speak about their prognostic significance on our clinical material.

Our positive prognostic factors that are significant for the treatment of patients with NSCLC are:

Stage I – IIIa, performance status <2 (ECOG), and age <60 – for resectable NSCLC and Stage IIIb, performance status <2 (ECOG), age <70 and loss body mass up to 5.5kg – for local advance NSCLC. Elevate of serum level of LDH and leucocytosis in this stage of NSCLC is result: extent of disease, metastatic disease and bad final issue.

***Key words:*** **NSCLC (Non-small Cell Lung Cancer), performans status, stage, LDH, leucocytosis.**

Non-Small Cell Lung Carcinoma (NSCLC) today, mainly enclose the non-small cell carcinoma, adenocarcinoma and carcinoma of large cells. Unfortunately, in majority of patients, in the moment of making of diagnosis, disease is in the stage that is loss for surgical treatment. In spite of developing the new chemotherapy agents and strategies of the multimode treatments, the survival rate in the several last decades stay unchanged and very poor. In the big series of unselected patients, the five years survival is between 4 and 7%, regardless of which kind the treatment was made[1, 2]. Between the patients from the Clinic of Lung Diseases and TB "Podhrastovi" the five years survival was 2.1%. A relatively small group patient has been diagnosed in the stage of surgically acceptable disease. But and in the cases of patients who can consider as potentially cured, after radical surgical treatment, only one third of them will be on live after 5 years from surgery. On the other side, even at the patients which tumors similar like surgically respectable, majority of them already has disseminated metastases. The important differentiations were evidence between tumors with and without squamous differentiation[3], but and within every

subgroup of NSCLC there is significant variability in the view of clinical behave[4].

In the treatment of NSCLC, there would be very important identification of reliable predictors of survival and effects on chemotherapy. It would be make easier and better identification of patients who could have benefit from additional treatment with chemotherapy. On the other side it could help knowledge for omission chemotherapy at the patients who have minimally chances for benefit.

In generally, prognostic factors of NSCLC could be divided in prognostic factors before the treatment and prognostic factors that are in connection with therapy of locally advanced NSCLC.

The problem that we will elaborate here are pretreatment prognostic factors.
They could be classified in four great groups:
Pretreatment clinical prognostic factors for NSCLC,
Standard biological factors,
Pathological factors and
Molecular - biological factors.

Today, in routinely work in Bosnia and Herzegovina, in estimating of prognosis of NSCLC we mainly using clinical factors and in limited number of cases biological and pathological factors. In this article during the evaluation of each factor we will present and our own results.

**Patients and methods**

Our own experiences are based on elaboration of 67 patients with NSCLC, diagnosed and treated on Clinic of Lung Diseases and TB "Podhrastovi", and less number of them on Clinic for Thoracic Surgery and Institute for Oncology of Clinical Center University of Sarajevo. Histology examination was made on Institute for Pathology of Medical Faculty University of Sarajevo.

In estimated group, by sex, there were 50 male and 17 female patients (index = 3:1), age 58.4±12.6 (range 26 – 74).

By histology type in 48 cases there were small-cell carcinoma, 18 cases with adenocarcinoma and 1 case was carcinoma of large cells.

By stage of disease there was:

| | | |
|---|---|---|
| - Loco-regional disease | (St. I – IIIa) | 10 pts = 15% |
| - Locally advanced disease | (St. IIIb) | 43 pts = 64% |
| - Metastatic disease | (St. IV) | 14 pts = 21% |

## Results

### Clinical pretreatment prognostic factors for NSCLC

The most important prognostic factors are showed on table 1.

Table 1: Prognostic factors for NSCLC

| |
|---|
| TNM stage |
| Performance status |
| Sex |
| Age |
| Loss on weight |
| Increase of level of LDH (Lactate dehydrogenises) |
| Histology type |



TNM stages – Expansion of Disease

TNM stages giving the answer on question: "Where is disease in body, on which places?" Today, there is too much polemics about prognosis of NSCLC. But all of them are agree about fact that earlier stages of NSCLC providing a longer survival and better prognosis.

This fact corroborates all studies worked on this theme up to now. On the basis a more studies, the Britons[5] were worked a table of 5-year survival patients with NSCLC, by stages of this disease, and which is very similar with some from the other develop countries (table 2).

Performance status (PS)

Together with the stage of expansion of tumor, performance status is very important prognostic factor. The poor PS providing a high risk for death and without progression of disease. In study of Movsas et all[6] the patients with low PS (Karnofski index = 50-70%) were treated with chemo-radio therapy and they had the lowest mean survival (7.8 months) and the lowest a quality time of survival (6.7 months).

Table 2: Staging by groups and prognosis of NSCLC in Great Britain and patients of Clinic for Lung Diseases and TB – 2000.

| Stages | TNM subgroup | 5-year survival in % | 1 year % | 2 year % | 3 year % |
|---|---|---|---|---|---|
| | Carcinoma In situ | | | | |
| IA | T1 N0 M0 | 61 | | | |
| IB | T2 N0 M0 | 38 | | | |
| IIA | T1 N1 M0 | 34 | | | |
| IIB | T2 N1 M0 | 24 | 27 | 90 | 70 | 60 |
| | T3 N0 M0 | 22 | | | |
| IIIA | T3 N1 M0 | 9 | | | |
| | T1 N2 M0 | 13 | | | |
| | T2 N2 M0 | 13 | | | |
| | T3 N2 M0 | | | | |
| IIIB | T4 N0 M0 | | | | |
| | T4 N1 M0 | 7 | | | |
| | T4 N2 M0 | | | | |
| | T1 N3 M0 | | 5 | 67.4 | 30.3 | 11.6 |
| | T2 N3 M0 | | | | |
| | T3 N3 M0 | 3 | | | |
| | T4 N3 M0 | | | | |
| IV | anyT & any N M1 | 1 | 7.14 | - | - | |



The PS has the goal to give the answer on question how disease influencing on vital daily activity of patients, with the aim of definition of real treatment and prognosis. There are two ways of definition of PS (Karnofski index and ECOG table of PS which is presented in table 3).

Table 3: ECOG Performance status

| Grade | |
|---|---|
| 0 | Full activity, without restrictions (as before disease) |
| 1 | Restricted fisical activity, but able for ambulatory treatment, patient is able for easier work (easy home work, work in office and similary) |
| 2 | Ambulatory patient which is able to take care about himself , but he/she is not able for any work activity. He/she spending more than 50% time out of bed. |
| 3 | Patient is able only for restricted care about himself. He/she spending in chair or in bed more than 50% time per day. |
| 4 | Fully inactivity. He/she is not able to take care about himself/herself. Patient is fully band for the bed or chair. |
| 5 | Death |

Fig 1: Relation of overall survival and PS for st. I-IIIa
PS on patients Clinic of Lung Diseases and TB

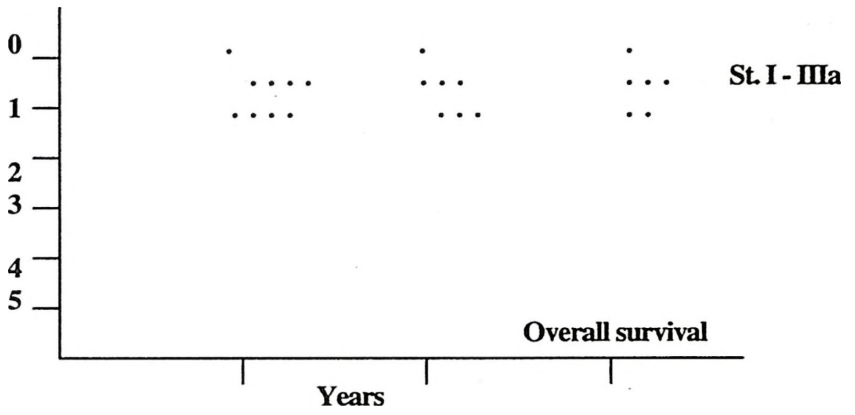
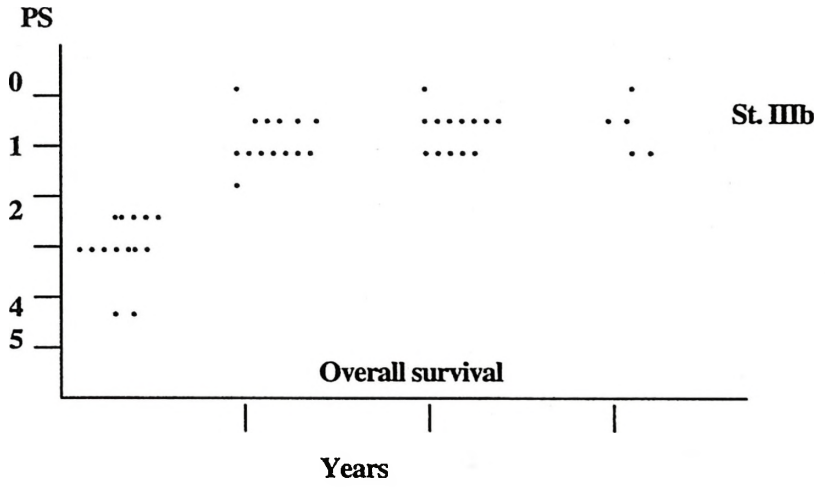
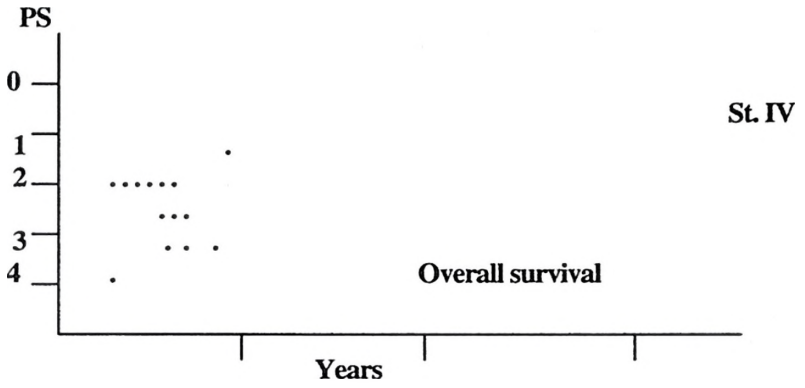



Fig 2: Relation of overall survival and PS for st. IIIb
on patients Clinic of Lung Diseases and TB




As it presented on Figs. 2 and 3, our patients with PS<3 (ECOG), had overall survival less than one year.

Fig 3: Relation of overall survival and PS for st. IV
on patients Clinic of Lung Diseases and TB




Sex as an prognostic factor

The International Association for the Study of Lung Cancer (IASCL) indicated sex as a possible prognostic factor[7]. Today, usually this is linkage for the role of female sexual hormones, which is still not completely illuminated. There are two facts that are in relation with female sexual hormones. One is "the protecting role" of female sexual hormones in relation to tobacco smoking and the second is a longer overall survival of female patients with NSCLC. Our observations don't corroborating these facts.

**Age as prognostic factor**

Some indicated only a minor influence of age as a prognostic factor. The reason for that is co morbidity at the older patients (>70 y). It's cardiovascular diseases, COPD, diseases that disturb renal function, diabetes mellitus, the general fall of functional status, arthritis's and peripheral vascular diseases.

The percentage of survival by stage and age of patients with NSCLC, in our study population is showed on the tables 4, 5 and 6.

Table 4: Percentage of survival by age.
Patients treated surgery only
– Stage I – IIIA

| Age | N | Percentage of survival 1 y | 2 y | 3 y |
|---|---|---|---|---|
| 21 - 31 | 2 | 50 | 50 | 50 |
| 31 – 40 | 1 | 100 | - | - |
| 41 – 50 | 3 | 100 | 100 | 66.6 |
| 51 – 60 | 3 | 100 | 100 | 100 |
| 61 – 70 | 1 | - | - | - |
| 71 – 80 | - | - | - | - |

Table 5: Percentage of survival by age
Treated by chemo-radio therapy
– Stage III b

| Age | N | Percentage of survival 1 y | 2 y | 3 y |
|---|---|---|---|---|
| 21 - 31 | 2 | 100 | - | - |
| 31 – 40 | 4 | 50 | - | - |
| 41 – 50 | 8 | 62.5 | 37.5 | 12.5 |
| 51 – 60 | 14 | 71.5 | 35.7 | 14.3 |

Table 6: Percentage of survival by age.
Treated by chemo-radio therapy
- Stage IV

| Age | N | Percentage of survival 1 y | 2 y | 3 y |
|---|---|---|---|---|
| 21 - 31 | - | - | - | - |
| 31 – 40 | 1 | - | - | - |
| 41 – 50 | 2 | - | - | - |
| 51 – 60 | 5 | - | - | - |
| 61 – 70 | 5 | 20 | - | - |
| 71 – 80 | 1 | - | - | - |



As it's showed on tables 4, 5 and 6 in our sample patients with resectable NSCLC, age till 60 is a good prognostic factor. For locally advanced disease, age till 70 with chemo-radio therapy is still a good prognostic factor (two years survival is 40%).

Total weight loss

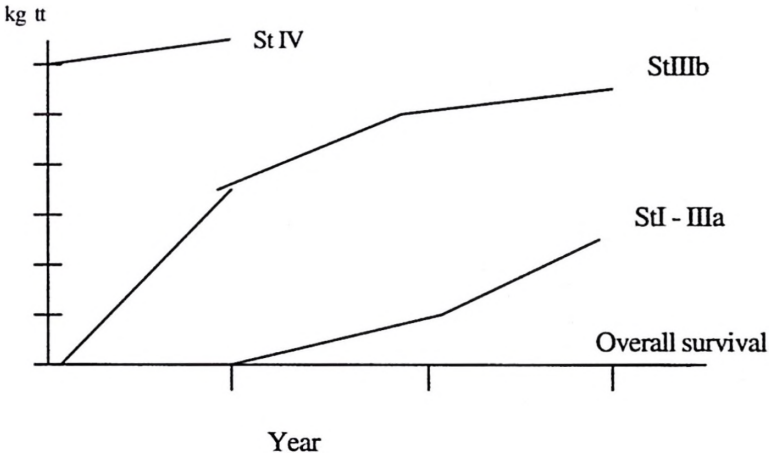
Total weight loss till the final diagnosis also is not neglect prognostic factor. The total weight loss is reflection of general influence of the disease. The most commonly adopted definition of weight loss from 4.53 kg in recent studies is changed with definition that it is loss on weight 5 - 10%, from the weight 6 months before the diagnosis.

Our results (table 5 and figure 4) showing that the total weight loss is proportional to overall survival and stage of disease. The advanced stages of disease are characterized with the bigger median total weight loss.

Table 5: The median weight loss by stages of median loss disease and years of overall survival

| Stage | N | 1 y | 2 y | 3 y |
|---|---|---|---|---|
| I - IIIa | 10 | 0 kg | 0.8 kg | 3.4 kg |
| IIIb | 43 | 4.5 kg | 5.3 kg | 5.5 kg |
| IV | 14 | 6.8 kg | | |

Fig. 4: The overall survival and median loss on weight by stages of disease





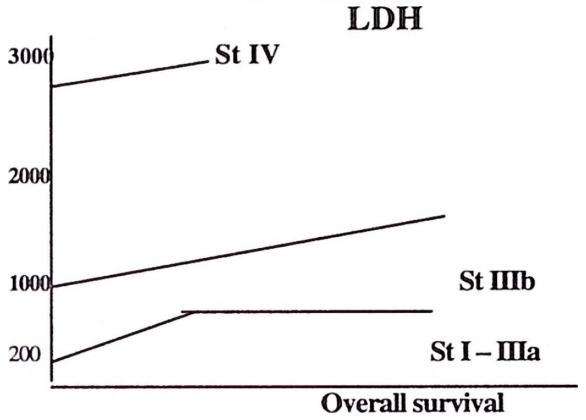

Pretreatment serum LDH

The level of pretreatment serum lactate dehydrogenase (LDH) at the patients with NSCLC seems to reflect the overall tumor burden and may therefore be of major influence on long-term survival for the patients with NSCLC.
Our results are showed on table 6 and figure 5.

Tabela 6: Pretreatment serum LDH and overall survival by stages of disease

| Stage | 1 y | 2 y | 3 y |
|---|---|---|---|
| I – IIIa | 280±167 | 275±177 | 290±192 |
| IIIb | 348±162 | 556±74 | 682±82 |
| IV | 2703±885 | | |

**Fig 5:** Pretreatment serum LDH and overall survival by stages of disease




Range for serum LDH in our laboratory is 230 – 460 U/L. There is evidence from results given in table 6 and figure 5 that increase of the level serum LDH is reflect of stage of disease (locally advanced and metastatic stage).

Histological types as prognostic factor of NSCLC

In discussion about prognosis of NSCLC, the data about metastasis on the other distant locations are very important. Today, it's known that adenocarcinoma showed a less locally progression and relatively quickly expansion in a brain and the other distant localizations. Different from it, the squamous cell carcinoma showed a poor tendency for distant metastases and more widening in locally advance.

When histology is in function of prognosis, there is very important fact that the growth of lung cancer has exponential character and the time of survival, in the moment of making the diagnosis, is in function of size of tumor, respectively of its double increasing[8]. For small-cell carcinoma, the time of double increase of tumor is about 50 days, for squamous and large cells carcinomas about 100 days, and for adenocarcinomas is about 80 days[9, 10]. In the case of lung cancers, some calculated that the tumor cell with diameter from 10μm producing a node with diameter of 1 cm for about 1 year, and after 30 multiplications. Starting with this fact, extrapolation to backwards, some studies showed that slow growing tumors, as squamous lung carcinomas and adenocarcinomas could be present in lungs of patients 8 – 15 years before the making of diagnosis, and in the cases of small cell carcinoma, 3 years ago[11]. It could be meaning that natural course of lung cancer is characterized with unrecognizing growth, and that is

clinically recognized a short time before the lethal end. Because of that, the clinics has a very short time to do something, and that is reason why the all clinical stages of this disease could be consider as the last stage. It's very disappointing to accept the fact that even on beginning twenty-first century we don't have the efficacy methods for detection of disease in pre-clinical stage.

**Biological pretreatment prognostic factors for NSCLC**

Leucocytes

Pretherapeutic absolute white blood cell and relative neutrophil counts were considered as abnormal if $> 10x10^3$ cells/$\mu L^{-1}$ and > 75% of the total white blood cells were present, respectively. Both abnormal white blood cell and neutrophil counts were identified as poor prognostic factors (median survival times of 24 – 32 weeks). Even that, the increased white blood cells and neutrophil counts could be the sign of the infection of lower respiratory tract which is in connection with tumor, what making the prognosis worse.

Standard serum tumor markers

Such substances are tumor-specific and can be produced by one, few, or several types of cancer. Other substances are produced by tumor cells in larger amounts than by normal cells. Occasionally, normal cells release abnormal quantities of their products in response to invasion by cancer cells.

Lung tumor markers fall into several categories, including oncofoetal proteins, structural proteins, enzymes, membrane antigens, peptide and nonpeptide hormones and other tumor-associated antigens. They may play different roles in clinical practice including the assessment of prognosis.

At least three classes of tumor markers have prognostic significance in NSCLC, even about that the opinions of many experts are divided. It is carcinoembryonic antigen (CEA) and two cytokeratin-derived markers: tissue polypeptide antigen (TPA) and Cyfra 21. These tumor markers may predict clinical outcome mainly because their evaluation correlates with the tumor mass and malignant potential of the tumor.

In a recent French study on the prognostic value of six different tumor markers, the analysis was based on multivariate models of survival[13]. It was found that, besides metastases (p=0.017) and CEA125 (p=0.03) were significantly correlated with the outcome of 88 nonsurgical NSCLC patients. Furthermore,

elevated levels of Cyfra 21-1 during the course of disease were also an independent predictor of poor survival. In a recent study on lung cancer prognosis[14] 1296 consecutive patients seen over a 16-yr period were analyzed by Cox regression models. In every multivariate test, TPA emerged as being among the most important predictors of survival. Depending on the combination of variables in the model, TPA proved to be the second most important factor after either stage or performance status, and in front the other important clinical factors, such as the number and type of metastatic sites, the T and N factors, or the weight loss.

Even that, today on global level therefore has not consensus about prognostic role of tumor markers at the NSCLC.

**Pathological pretreatment prognostic factors for NSCLC**

In a multivariate model of recurrence of the Lung Cancer Study Group based on 392 stage- I NSCLC cases with final pathological review, it was reported that patients with squamous cell tumors had a lower risk of recurrence and tumor-related death[15]. As well as in the Leuven Lung Cancer Group experience on 140 surgically treated patients with IIIA-N2 NSCLC, patients with non-squamous cell tumors had a significantly increased risk of tumor-related death. Regarding relapse patterns, different authors suggested that squamous cell tumors are more prone to locoregional recurrence and adenocarcinomas to distant recurrence[16, 17, 18]

The results received by comparison of average time of survival and pathological type of tumors, from patients of Clinic of Lung Diseases and TB are showed on table 7, 8 and 9.

Table 7: Median time of survival by pathological type of tumor

St. I – IIIa; N=10 (Pts. of Clinic of Lung Diseases and TB)

| Pathological type | Squamous | Adenocarcinoma | Large cells carcinoma |
|---|---|---|---|
| No patients | 6 | 3 | 1 |
| Average time of survival in months | 39.3 | 24.6 | 10 |

p= 0.003 ($\alpha$=0.05)

Table 8: Median time of survival by pathological type of tumor

St. IIIb; N=43 (Pts. of Clinic of Lung Diseases and TB)

| Pathological type | Squamous | Adenocarcinoma |
|---|---|---|
| No patients | 31 | 12 |
| Average time of survival in months | 27.2 | 20.3 |

p= 0.009 ($\alpha$=0.05)

Table 9: Median time of survival by pathological type of tumor

St. IV; N=43 (Pts. of Clinic of Lung Diseases and TB)

| Pathological type | Squamous | Adenocarcinoma |
|---|---|---|
| No patients | 10 | 3 |
| Average time of survival in months | 11 | 8.2 |

p= 0.032 ($\alpha$=0.05)

As it showed in tables 7, 8 and 9, patients with squamous cell carcinoma had statistically significant a longer median time of survival, regardless on stage of disease.

The absence of differentiation and presence of lymphatic and blood vessel invasion are significant elements of aggressively of lung tumors. On the basis of light microscopy, the differences could be make on: good, median, small or none differentiation of lung cancers. Small differentiation is associated with poor survival from NSCLC[19, 20].

But, presence of blood vessel invasion is a better prognostic factor than differentiation of lung tumors. Many studies are evidenced that the presence of blood vessel invasion was associated with decreased survival. In a US study on 289 consecutive stage-I NSCLC patients, vascular invasion proved to be of significant prognostic value both in univariate ($p<0.01$) and multivariate (p $p<0.05$) analyses[19]. A French group reported that venous but not arterial invasion correlated with the T-factor and p-TNM, whereas lymphatic vessel invasion correlated with the N-factor and p-TNM[20]. In their multivariate model on 96 resected NSCLC patients, lymphatic vessel invasion and p-TNM were important predictors for poor disease-free and overall survival.

## Discussion

Our financial conditions don't allow us molecular-biological studies concerning determination of diagnostic and prognostic values some cellular molecules

respectively of gene abnormalities. Concerning that, in the western countries today, they making the investigations of the role of angioneogenesis, as well as investigations of prognostic value of activation of K-Ras oncogene, p53, p16 and the other gene abnormalities, and the level of neuron specific enolasis. On this place we will give just explanation of their role in the prognosis of NSCLC.

Molecular-biologic pretreatment prognostic factors

Neoangiogenesis

The observation of increased microvessel density in tumors not only serves as an independent prognostic indicator, but also suggests that antiangiogenic therapy may be an important component of treatment regimes for cancer patients[21]. Many positive regulators, including growth factor receptors, matrix metalloproteinases, and integrins, have been correlated with increased vascularity of tumors and poor prognosis for patient survival. Thus, these mediators may represent ideal targets for antiangiogenic therapy[22]. In tumor samples, neoangiogenesis may be evaluated as vascular density and as expression of angiogenic regulators, and both these methods may provide useful indications from a prognostic point of view[23].

In a series of 407 NSCLC, the number of microvessels was significantly associated with poor prognosis in terms of overall survival[24]. Angiogenesis was quantified as microvessel count and the median value of this series was 20 vessels. In the univariate analysis, patients with larger tumors, more advanced stage, greater degree of regional lymph node involvement, or more vascular tumors experienced reduced overall survival.

Vascular endothelial factor of growth (VEGF) is one of the most important tumor-derived cytokines that contributes to the increased permeability of tumor vasculature, and which shows a mitogenic activity on endothelial cells. A great number of studies demonstrate its influence in lung cancer progression and poor overall survival of the host[25].

K-Ras oncogen activation

In the NSCLC, the family of mutant oncogens is part of Ras family the small G proteins that have influence on cell growth. This including: N-Ras, K-Ras, H-Ras protooncogens and their activity are mediated by guanin-nucleotid changeable factors (GEF), which changes guanozindiphosphate (GDP) in guanozintriphosphate (GTP). Ras family of protoncogens has a role in

transmission the signals of growth from cell surface to nucleus. In the cells this protooncogen is finding in inactivated GDP form. As the answer on linkage of ligands on the cell receptors, Ras family of protooncogens being activate only transient, but in the cases of mutation this protooncogens in only one their amino acid part, they can locked in active position and on that way they beginning the oncogens.

Analysis of the rest of DNA by Ras protooncogen from lung cancer cells of humankind discovered the activating mutations of K-Ras oncogens. In adenocarcinoma its presence in 30%, and someone that investigated these mutations found that it has prognostic significance[26, 27].

In a study of 69 patients with totally resected tumor (adenocarcinoma) the authors found significant decrease of K-Ras mutations in patients who had a longer overall survival, and disease free survival[28]. Mitsumi et al[29] were showed that patients with early and late stages of NSCLC but and positive Ras mutations has a shorter time of survival in comparison whit these without mutations.

Prognostic value of p53 and p16 gene abnormalities

Among several genetic aberrations that have been implicated in lung cancer, alterations in the p53 and p16 tumor-suppressor genes are the most common.

Mutations in the p53 gene usually result in increased steady-state levels of p53, which may play role in carcinogenesis through transdominant mechanisms, perhaps involving oligomerisation between mutant and wild type proteins. During the last 10 years, a large number of studies have evaluated p53 alterations in lung cancer[30]. Some studies have demonstrated that a p53 mutation is associated with poor prognosis of NSCLC[31, 32], while others have reported no significant effect[33], or have even concluded that p53 protein overexpression can be a good prognostic characteristic[34].

Genetically, the p16 gene can be inactivated by point mutation or homozygous deletion, as observed in various human primary tumors, including lung cancer. Recently, Belinsky et al[35] showed, for the first time, that inactivation of p16 gene by aberrant methylation is an early and likely critical event in the development of lung cancer.

In a group of 98 surgically treated stage I-IIIA NSCLC patients, p53 mutations were detected in 46 (47%) cases (point mutations in 8 and promoter hypermethylation in 34). No correlation was found between p53 and p16

abnormalities and various clinicohistological factors, including age, sex, histological type of tumor and TNOM stage.

Survival analysis revealed that both the patients with p53 and p16 abnormalities tended to have poorer prognosis than the patients without p53 (p=0.02) and P16 (p=0.01) abnormalities. In the multivariate analysis, however, when the types of p16 inactivation were analyzed, p16 hypermethylation rather than point mutation was associated with poor prognosis[33].

Evaluation of p53 by yeast functional assay was performed in 42 patients. Twenty-seven of the 42 (64%) NSCLC samples contained mutant p53 in the yeast functional assay with the higher frequency in squamous cell carcinoma (16 of 22 (73%)) than in large cell carcinoma (4 of 7 (57%)) and adenocarcinoma (7 of 13 (54%; p<0.02)). Preliminary prognostic analysis showed that patients scoring positive for yeast test had significantly shorter disease-free survival (median 11 months) than those that scored negative (median 23 months)[36].

**Conclusions**

On the basis the clinical, biological and pathological pretreatment factors of NSCLC, in everyday praxis, we can say something about the prognosis of the NSCLC. Molecular-biological pretreatment factors are not in the routine praxis. On sample of 67 patients with NSCLC, from Clinic of Lung Diseases and TB, Clinical Center University of Sarajevo, the authors are proved the next:

a) The possibility of survival with today's therapeutic treatment are:
- stage I – IIIA : 1-year 90%, 2 – year 70%, 3 – year 60%;
- stage IIIB : 1-year 67.4%, 2 – year 30.3%, 3 – year 11.6%;
- stage IV : 1-year 7.14%

b) The patients with stage I-IIIA had PS 0 – 1,
- stage IIIB had PS 1 – 4,
- stage IV had PS 2 – 4.

c) Age till 60 is a good prognostic factor for the three years survival for the resectable NSCLC. In the cases patients with locally advanced NSCLC, the age from 70 is a good prognostic factor for the two years survival with the chemo radiotherapy treatment.

d) The more median weight loss is linkage with the higher stage of disease and less survival; weights loss more than 5.5 kilograms suggest for the metastatic stage of disease.
e) We were finding the increase of serum LDH more than its referent values at the locally advanced disease. Increasing of serum LDH more than double referent value is suggesting for the metastatic disease.
f) White blood cells number more than $10x10^6$/ml and percentage of neutrophils more than 75% are poor prognostic factors for NSCLC.
g) Squamous cell carcinoma has a better prognosis concerning the overall survival than adenocarcinoma and large cell cancer regardless on stages of disease.

Accordingly, the positive prognostic factors that are significant for the treatment patients with resectable NSCLC are: stage of disease I – IIIA, PS<2 (ECOG), and age of patients (less than 60).

For locally advanced disease the main prognostic factors are: stage of disease IIIB, PS<2 (ECOG), age of patient (less than 70), weight loss till 5.5kg. High level of serum LDH and increase number of white blood cells in this stage of disease are result of tumor growth and his metastatic widening. We could say that this factors condemning in advance the therapeutic approaches.

**Sažetak**

U posljednjoj deceniji skupina novijih prognostičkih faktora dodana je listi dobro poznatih kliničkih prognostičkih faktora za nemikrostanični rak pluća (NSCLC). Među novijim izdvajaju se: mutacije u K-*ras* onkogenu, abnormalni p53 proteini kao posljedica mutacija na p53 supresorkom genu, imunohistohemijskim bojenjem dokazano prisustvo adhezivnih
molekula neuralnih stanica kičme (N-CAM), porast serumskog nivoa neuron specifične enolaze (NSE) i slično.

U današnjim uslovima u BiH navedeni biomarkeri još uvijek nisu našli svoje mjesto u svakodnevnoj kliničkoj praksi. To je razlog zašto ne možemo govoriti o njihovom značaju u prognostičkom smislu na našem kliničkom materijalu.

Naši pozitivni prognostički faktori od značaja za dalji tretman pacijenata sa NSCLC još uvijek se odnose na:

stadij bolesti I – IIIa, performans status < 2 (ECOG) i dob pacijenta <60g – za resektabilni NSCLC, te

stadij bolesti IIIb, performans status < 2 (ECOG), dob pacijenta <70g i gubitak na tjelesnoj težini do 5.5kg – za napredovali NSCLC. Porast nivoa serumske LDH i leukocitoza u ovom stadiju bolesti prvenstveno su odraz napretka u rastu tumora, metastaziranja i moglo bi se reći da unaprijed osuđuju terapijski pristup na neuspjeh.

***Ključne riječi:*** NSCLC (nemikrostanični plućni rak), performans status, stadij bolesti, LDH (laktat dehidrogenaza), leukocitoza.

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