Locally advanced non-small cell lung cancer - pretreatment prognostic factors: Disease stage, tumor histopathological characteristics, the patient-related factors

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SUMMARY

Background: *The existing tumor-node-metastasis staging system ignores numerous clinical, therapeutic, and biological characteristics of lung cancer and psychomotor condition of a patient because it is based on the anatomic extent of disease. Therefore, there is a possibility of inadequate choice of therapy for any individual patient. Based on the disease stage, histopathological characteristics of the tumor and the patient-related factors (sex, age, Karnofsky status, accompanying diseases) the outcome of the disease can be predicted in patients with inoperable and unresectable non-small lung cancer.*

Methods: *This report is a prospective clinical study that included patients with histopathological verified non-small cell lung cancer, followed up for a six-month period, from the beginning of the treatment. The following data were recorded: sex, age, histological cancer type, stage, Karnofsky status, and comorbid diseases.*

Results: *The study showed planocellular carcinoma was more dominant among men than among women and that and at the diagnosis, most patients were in IIIb or IV stage. There was a decrease in psychomotor status of patients. The length of survival depended on Karnofsky index ($p = 0.000$), comorbidities – chronic myocardiopathy ($p = 0.001$), diabetes mellitus type 2 ($p = 0.007$), myocardial infraction ($p = 0.005$), and the stage of the disease ($p = 0.001$)*

Conclusion: *Psychomotor status of a patient, comborid diseases, and the stage of disease are the factors that determine patient's tolerance to oncology treatment.*

Key words: *Carcinoma, Non-Small-Cell Lung; Neoplasm Staging; Prognosis; Karnofsky Performance Status; Comorbidity; Age Factors; Sex Factor; Psychomotor Performance; Neoplasms by Histologic Type*

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INTRODUCTION

The existing tumor-node-metastasis (TNM) staging system ignores numerous clinical, therapeutic and biological characteristics of lung cancer and psychomotor condition of the patient because it is based on the anatomic extent of disease (1). Therefore, differences in the length of survival of the patients within the same stage of the disease reflect the effects of these variables.

The importance of these parameters in every day practice is emphasized by many studies. Wigren et al. point out the importance of prognostic factors – extent of the disease, Feinstein scale of clinical symptoms, performance status, tumor size, and hemoglobin level. In addition to these factors, research based on VALG (Veterans Administration Lung Group) protocol includes accompanying diseases as a significant prognostic factor. One of the most comprehensive studies on prognostic factors was carried out by Maki and Feld, who by means of meta-analysis overviewed 20 studies on prognostic factors. According to results obtained by multifactor analysis, it can be concluded that stage of the illness, together with performance status and loss in weight, is an important prognostic factor. Age and the histological type of cancer seem to have little or no influence on survival, while the significance of sex remains inconclusive (2,3).

Based on the disease stage, histopathological characteristics (PH) of the tumor and the patient-related factors (sex, age, Karnofsky status, accompanying diseases) the outcome of the disease can be predicted in patients with inoperable and unresectable non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

This review is a prospective clinical study carried out from May 2005 to December 2006, which included 87 patients with histopatologically verified non-microcellular lung cancer in stage III and IV. The follow-up period was six months, from the moment the diagnosis was established and the treatment started. The follow up visits were scheduled every 60 days from the beginning of oncological treatment i.e., from the moment they were included in the study. All values are expressed as mean ± standard deviation (SD). Commercial SPSS (Statistical Package for the Social Sciences) version 11.0 for Windows was used for the statistical analysis. Statistical evaluation was performed by Student's t test for paired observations, one-factorial and two-factorial analysis of variance, χ^2 test, Fisher's test, Mann-Whitney and Kruskal-Wallis tests, Spearman test for linear correlation, Kaplan-Meir method and Cox regression for survival testing. The differences were considered significant when p value was less than 0.05 and highly significant when p value was less than 0.01 (4).

RESULTS

Eighty-seven inoperable and unresectable patients diagnosed with non-small cell lung cancer were studied. There were 75 (86.2%) men and 12 (13.8%) women. The ratio between male and female sex was 6.25 : 1.

The average age of the patients was 63.7 years. The youngest patient was 47, and the oldest was 86. The average age of men was 63.8 (SD = ±10.5),

while for women, it was 62.7 (SD = ±5.8). There was no significant difference between male and female average age (p= 0.721).

There were more patients (62) with planocellular carcinoma than with adenocarcinoma (25). None of the patients had large-cell cancer. A statistically significant difference was found between male and female sex in relation to the histological type of cancer (p= 0.004). Women had eight times greater risk of developing an adenocarcinoma than men. The average age of the patients with planocellular carcinoma, regardless of the sex, was 65.7 (10.2), while the average age of the patients with adenocarcinoma was 58.7 (7.5). There was a statistically significant difference between the age of the patients related to the type of the cancer (p= 0.004). Elderly people run a smaller risk (0.907) of developing an adenocarcinoma than planocellular.

Eight patients (2 women and 6 men) were in stage IIIa, with the average age of 66.3 years (7.4). With IIIb stage, there were 44 patients (6 women and 38 men) of the average age of 62.5 years (8.8). With the disease diagnosed in stage IV, there were 35 patients with average age of 64.5 years (11.8) – 4 women and 31 men. There was no statistically significant correlation between the age of the patients and the stage of the disease at the moment of diagnosis (p= 0.515), nor between PH type of the cancer and the stage of the disease at the moment of diagnosis (p= 0.361).

Performance status was assessed by means of Karnofsky Scale (0-100) at the moment the treatment started. The median value of Karnofsky performance status among the female patients was 65 (52.5-85.0), and among male patients, it was 70 (50.0 – 70.0). There was no statistically significant difference in Karnofsky status between the sexes (p= 0.572). Lower values of Karnofsky status corresponded to higher age of the patients (r = -0.221, p= 0.040). When we compared the median value of Karnofsky performance status in relation to the PH type of cancer, there was no statistically significant difference (p= 0.566). However, correlation between the stage of the disease and the performance status by Karnofsky was statistically significant (p= 0.000). The median value of Karnofsky status was 70 (62.5 -80.0) in patients with IIIa stage, 70.0 (70.0 -70.0) in patients with stage IIIb and 50.0 (40.0 – 60.0) in patients with stage IV.

Table 1. Comorbidity according to age

Comorbidity	Number of patient	Average age (SD)
Myocardial infraction	5	70.4 (6.5)
Diabetes mellitus type 2	11	72.2 (6.1)
Arterial hypertension	16	69.1 (8.7)
TBC fibrocaseous	2	70.0 (1.0)
Chronic pulmonary obstructive disease	6	62.7 (13.0)
Chronic myocardiopathy	5	73.8 (13.4)
Brain infraction	5	69.2 (4.1)
Angina pectoris stable	2	78.5 (1.0)
Connective tissue disease	1	53
Chronic renal deficiency	3	61.0 (12.1)
Anemia (nonprimary)	3	61.0 (12.1)
Multiple sclerosis	1	68
Liver cirrhosis	3	65.3 (12.1)

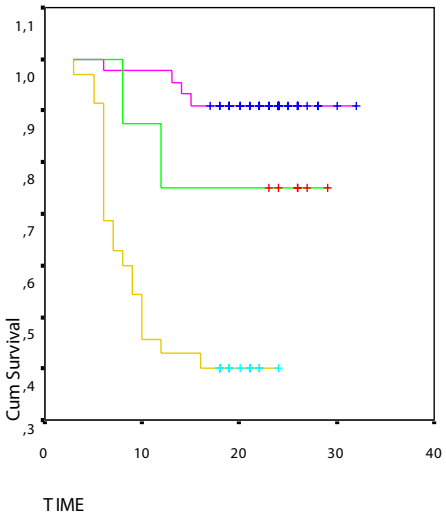
Investigation of the linear correlation between the age and Karnofsky value yields r = -0.221 and p = 0.000, which means that lower the Karnofsky score corresponds to higher age of the patients. Older patients had diabetes mellitus (DM) type 2 (p = 0.002), artery hypertension (HTA) (p = 0.015), and myocardiopathia (MCP) (p = 0.019) (Table 1). Statistically significant correlation between Karnofsky status and comorbid diseases was found only in patients with obstructive disease (p = 0.032). The type of cancer did not depend on comorbid diseases.

However, it should be noted that diseases with a small sample (fewer than 5 cases) were not statistically analyzed because the obtained results would not be valid.

Median survival time for women was 17.5 weeks, and for men it was 21 weeks. There is no statistically significant difference (p = 0.333) between the median survival lengths in relation to sex. Shorter survival length corresponded to higher age (r = -0.435, p = 0.000).

Survival did not depend on sex, there was no statistically significant difference (p = 0.457 by Kaplan-Meier).

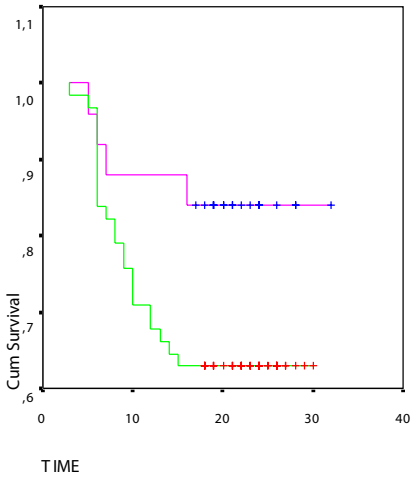
There was a linear correlation between Karnofsky performance status and the length of survival (p = 0.000, r = 0.835). Higher Karnofsky scores corresponded to longer survival length. The risk of dying in stage IIIb and stage IV depended on Karnofsky score, calculated based on Cox regression (p IIIa = 0.230, p IIIb = 0.037, p IV = 0.000). Median survival time was 25 weeks for patients in stage IIIa, 23.5 weeks for patients in stage IIIb; while for the patients in stage IV, it was 10 weeks. There was a statistically significant difference in the length of survival in relation to the stage of the disease (p = 0.001 by Kruskal- Wallis) (Figure 1). There was also a statistically significant difference in the length of survival between stages IIIa and IV (p = 0.079), and between stages IIIb and IV (p = 0.000). However, there was no statistically significant difference in survival between stages IIIa and IIIb (p = 0.164).



IIIa stage (green), IIIb stage (purple), IV stage (yellow)

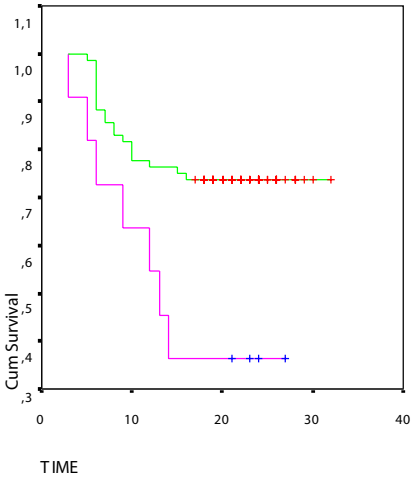
Figure 1. Relationship of survival patients with non-small cell lung cancer according to stage disease

Only in stage IV, there was a statistically significant difference in survival in relation to the PH diagnosis of the disease (p IIIa = 0.392, p IIIb = 0.267, p IV = 0.012) (Figure 2).



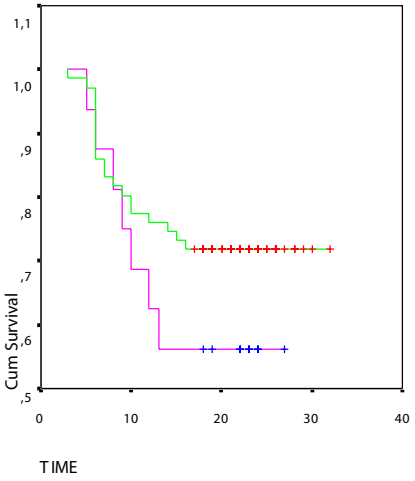
Adenocarcinoma (green), planocelullar carcinoma (purple)

Figure 2. Relationship of patients' survival with non-small cell lung cancer according to histological type of cancer



Without diabetes mellitus type 2 (green), with diabetes mellitus type 2 (purple)

Figure 3. Relationship of patients' survival with non-small cell lung cancer according to diabetes mellitus type 2



Without artery hypertension (green), with artery hypertension (purple)

Figure 4. Relationship of survival patients with non-small cell lung cancer according to artery hypertension

There was a statistically significant difference in survival of the patients in relation to myocardial infarction ($p = 0.005$), DM type 2 ($p = 0.007$) (Figure 3) and MCP ($p = 0.001$). There was no statistically significant difference in survival in relation to HTA ($p = 0.241$) (Figure 4), obstructive disease (HOBP) ($p = 0.259$) and infarctus cerebri (CVI) ($p = 0.728$). According to Cox multiple regression, the risk of death within a certain time period was higher in women ($r = 10.03$) and in elderly people, and it was less in patients with adenocarcinoma ($r = 0.159$) and in patients with higher Karnofsky scores ($r = 0.816$).

DISCUSSION

More men than women are affected with non-small cell lung cancer, and there is a statistically significant difference of the histological type of cancer in relation to the sex. This ratio is almost identical to the sex ratio concerning lung cancer in Serbia (5). According to the data of the European Association for Cancer Research and the American Oncology Society, the rate for women has been increasing in Western Europe and USA (6,7), which is not the case in our society. Together with the change in the sex ratio of patients with lung cancer, PH distribution changes – the number of patients with adenocarcinoma of non-small cell lung cancer increases. Planocellular carcinoma dominates in this sample of patients, which is yet another parameter different from the European Union. Increases in number of female patients and in number patients with adenocarcinoma are explained by decrease in smoking rates, and by other factors that dominate in cancerogenesis (e.g., hormonal factor). Our population is characterized with an increasing number of smokers, which can account for the greater number of men and the greater presence of planocellular carcinoma in the sample studied in this paper (7).

The risk of death in this sample is higher for women, which can be explained with their poorer psychomotor performance compared to men, and accompanying diseases that influence the length of survival. The risk of death due to adenocarcinoma is lower, although this type of carcinoma is dominant in female patients. The situation may seem illogical, but in fact, it is not because the type of cancer does not have an effect on the length of survival but only on the risk of dying at a certain moment.

Sex appears quite often as a prognostic factor (8-11), but the results are contradictory, even though it is defined as a prognostic factor by IASLC (International Association for Study of Lung Cancer). Most authors agree that female sex could be a favorable prognostic factor. In this study, sex is not to be taken as a prognostic factor with certainty.

There are some discrepancies in the published data concerning the length of survival of the patients with different histological types of non-small cell lung cancer, and there are also some data indicating that there are no differences in survival, i.e., that histological type is not a prognostic factor with patients that had not been operated on (9-14).

The greatest number of the studied patients had planocellular lung carcinoma, which is in accordance with the number of patients with this type of non-small cell cancer in Serbia (5). There is a statistically significant difference in distributions of the histological type of cancer in relation to the sex. There were more male patients with planocellular than with adenocarcinoma, while with women the situation was vice versa. In the literature, there are some discrepancies in prognosis for patients with lung cancers with different histological characteristics. Some studies have found longer survival time for patients

with planocellular carcinoma compared to patients with adenocarcinoma and large cell cancers, while other studies have found that patients with adenocarcinoma survive longer than do the patients with other types of non-small cell lung cancers. There are also some data indicating that there is no difference in the length of survival of the patients with non-small lung cancer, i.e., that the type of the cancer is not a significant prognostic factor, especially with patients that had been operated on (5,6,15).

Elderly patients represent a special problem in the field of oncology. More than 50% of these patients are over 65 years, and more than 60% of deaths due to malignancy fall into this category of patients. Older age is a risk factor for most of malignant diseases. It has been considered that ageing, i.e. decrease in functions of the immunological system in older age was responsible for this. It is now considered that tumors appear more frequently in elderly patients due to the time needed for the appearance of certain genetic changes leading to malignant alteration and for the tumor to become prominent enough; immunological changes have little or no effect on development of malignant diseases in elderly people (16-18).

The average age of the studied patients was 63.7 years, which means that they belong to the category of elderly patients. The age of 70 (or 60 by some authors) is generally considered the limit age for determining elderly patients.

Age has an effect on the course of the disease and the survival of patients with non-small cell lung cancer, but considering the immunological decline in elderly years, a question rises if it is due to the malignant disease itself and old age, or of accompanying diseases and decreased functions of vital organs. This question is even more interesting because based on some data younger patients with lung cancer have worse survival than the middle aged ones (8-10,19).

Age is a factor that cannot be with certainty classified as an independent prognostic factor because parameters of chronological and biological i.e. real age have not been defined yet. Chronological and biological age do not have to coincide, meaning that there are patients biologically younger (or older) than their chronological age. Necessity to determine biological age, i.e., discrepancy between biological and chronological age has lead to introduction of aging biomarkers. There are some disagreements about the criteria defining the biomarkers of aging, because it is not the only the issue of decline in functional performance in old age, but there are also some more complex parameters defining the changes in organism that lead to aging (17,18).

In this light, the factor of comorbid diseases can be a good clinical landmark for aging biomarker. For this reason, age is a dependant prognostic factor whose effects have to be considered only in correlation with comorbid diseases and based on which the most suitable oncological treatment will be determined.

A statistically significant relationship with the length of survival has been found in patients with prior myocardial infraction, diabetes mellitus type 2 and MCP. Other comorbid diseases were also diagnosed, but their significance is questionable because there were not numerous enough to be statistically important. However, the stated statistics is illustrative because it confirms the view held by many authors that comorbid diseases present an independent prognostic factor (9,20,21). Their significance as a prognostic factor has to be a clinically important parameter when an oncologist chooses a treatment modality. Analysis did not reveal a statistically significant correlation between accompanying diseases and the histological type of non-small cell lung cancer, which is very important because it points to other guidelines in investigation of etiology of non-small cell lung cancer. Because multicausality of this cancer is a well-established fact, the investigation should include endogenous factors, e.g., hereditary factors, metabolism disorders, endocrine status, decline in immunological defense system, and others.

Age has an effect on the course of disease and survival of the patients with non-small cell lung cancer, but considering the immunological decline in elderly years, the question rises if it is the result of the malignant disease itself and old age, or of accompanying diseases and decreased functions of vital organs. This question is even more interesting because based on some data younger patients with lung cancer have worse survival than the middle aged ones (8,9,19).

Since there is no statistically significant relation between histological type of cancer and Karnofsky status, it can be concluded that the type of cancer does not cause disorders in the psychophysical status of the patient (the linear relation between Karnofsky performance status and psychomotor status of the patients). It can be also concluded that decline in psychomotor functions occurs due to oncological and accompanying diseases. A statistically significant relation between the stage of the disease and Karnofsky index we found in our study and in literature (22-25) speaks in favor of this view.

Similar disease stage distributions were found in both male and female patients, which mean that there is no significant difference between sexes in relation to the stage of disease. In many studies, the average survival times of patients indicated that patients in stages I and II have better lengths of survival (22 and 13 months, respectively) compared to patients in stages IIIa, IIIb, and IV (8, 6 and 5 months). In this sense, the data we obtained are compliant with the data already given in the literature (25-27).

These data suggest that there is a need to perform a correct classification of patients, considering the fact that, within stage III, patients are classified as resectable or unresectable, and that all the treatment modalities are optional, especially with patients in stage IIIa.

These results confirm the existence of a constant dilemma that there is no significant difference in the length of survival between operable patients in stage III and patients under conservative treatment (27-35). Does it mean that the treatment modality is an independent prognostic factor in stage III, or is the difference in the length of survival influenced by some other factor? This question remains unanswered in this paper due to unproportional number of patients in stage IIIa and IIIb.

There are more and more suggestions that stage III should be divided into 4 subcategories, and our results speak in favor of these suggestions (21,25,26,32). It would mean a more precise triage of patients and a more purposeful treatment. Obviously, median survival time cannot be extended, but quality of life of patient can be improved. Since lung cancer patients usually belong to population of elderly people, further suppression of immune system of these patients would be avoided if aggressive modalities of oncological treatment were not applied (36,37).

CONCLUSION

Sex, age and histopathological type of the disease should not be the only guidelines in choosing the treatment because they do not show if the patient can endure aggressive oncological treatment i.e. compensatory strength of the organism, already weaken by the disease, can be spent, which will speed

up the inevitable end. Considering the aggressive nature of tumors and diagnosis in the advanced stages of the disease, determining factors in choosing the treatment modality should be psychomotor status, comorbid diseases and the stage of the disease.

Conflict of interest

We declare no conflicts of interest.

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