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Scientific Research

Forecasting of Survival Rate in Patients with the Early Stage of Non Small Cell Lung Cancer

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ABSTRACT

Lung cancer is the most common cause of death from oncological diseases all over the world. Primary treatment of patients with the early stage of non-small cell lung cancer is a surgery. However, after surgery 30% - 85% of patients undergo disease progression. In order to improve the results of treatment of patients with non-small cell lung cancer it is necessary to separate a group of patients with dismal prognosis for whom adjuvant chemotherapy will permit improving the survival rate. The aim of our research was to create a forecasting model with a view to detect the patients with the early stage of non-small cell lung cancer and dismal prognosis. Our research covered 254 patients with the early stage of non-small cell lung cancer who underwent a cure from June 2008 till December 2012 in the department of thoracic surgery of Zaporizhzhia Regional Clinical Oncologic Dispensary. In order to identify the factors connected with the risks of low survival rate of patients with the early stage of non-small cell lung cancer after curative treatment (surgical treatment, adjuvant chemotherapy), a method of design of neural network models of classification was used. 39 factors were taken for input characteristics. During investigation two forecasting models were built. As follows from the analysis of first forecasting model with the increase of the patient's BMI, the risk of low patient survival rate statistically and significantly ($p = 0.03$) decreases, OR = 0.89 (95% CI 0.80 - 0.99) for each kg/m2 index value. The risk of low patient survival rate also decreases ($p = 0.02$) if he has a squamous cell carcinoma, OR = 0.36 (95% CI 0.15 - 0.88) compared with other histological forms of tumor. The connection between the risk of low patient survival rate and the volume of surgical intervention was discovered ($p = 0.01$), OR = 3.19 (95% CI 1.29 - 7.86) for patients who underwent a pulmonectomy compared with patients who underwent an upper bilobectomy. As follows from the analysis of second forecasting model with the increase of the patient's BMI the risk of low patient survival rate statistically and significantly ($p = 0.01$) decreases; OR = 0.84 (95% CI 0.74 - 0.96) for each kg/m2 index value. It is found that with the increasing level of the EGFR expression in the primary tumor, the risk of low patient survival rate statistically and significantly increases ($p = 0.04$), OR = 1.39 (95% CI 1.01 - 1.90) for each graduation rate. The risk of low patient survival rate also increases when conducting the lymph dissection in the volume D0 - D1.

Keywords: Forecasting Model; Survival Rate; Non-Small Cell Lung Cancer

1. Introduction

Lung cancer is the most common cause of death from oncological diseases all over the world. Non Small Cell Lung Cancer (NSCLC) makes up 80% - 90% of all malignant neoplasm of lung. Primary treatment of patients with the early stage of NSCLC is a surgery. However after surgery 30% - 85% of patients undergo disease progression, wherefore five-year survival rate of this group of patients makes up 40% - 70%. Herewith 22% - 50% of patients have local regression, 48% - 78% have distant metastases and 3% - 20% of patients have simultaneous regression [1-5].

In order to improve the results of treatment of NSCLC patients, it is necessary to separate a group of patients with dismal prognosis for whom adjuvant chemotherapy will permit improving the survival rate [6]. The researches examining the efficacy of adjuvant chemother-

apy for NSCLC patients are not sufficient. These researches randomize about 8000 of patients during median term of monitoring of 5 years. By comparison, the research of adjuvant chemotherapy for breast cancer patients randomized over 100,000 patients during the term of monitoring for 15 years [3]. In this way it is obligatory to continue the efficiency of adjuvant chemotherapy for NSCLC patients. It has been stated that clinical staging is not appropriate for prognostication of risks of disease progression for early NSCLC patients [7]. Molecular markers may help separate a group of patients with dismal prognosis. The studies indicate that molecular markers may be useful for forecasting of the results of treatment and general survival rate of NSCLC patients [4, 8-11]. At present, a large number of markers are offered for NSCLC patients. However, none of them found its place in clinical practice [7]. Further studies of molecular predictive markers are required. Until then it is not advised to use them in routine practice [3].

Artificial neural networks have been used in a number of different ways in medicine and medically related fields. We have applied ANN to calculate the risk of NSCLC.

The aim of our research was to create a forecasting model with a view to detecting the patients with early NSCLC and dismal prognosis.

2. Materials and Methods

Our research covered 254 patients with the early stage of NSCLC who underwent a cure from June 2008 till December 2012 in the department of thoracic surgery of Zaporizhzhia Regional Clinical oncology dispensary. In order to identify the factors connected with the risks of low survival rate of patients with the early stage of NSCLC after curative treatment (surgical treatment, adjuvant chemotherapy), a method of design of neural network models of classification was used [5]. Binary variable Y represents the two outcomes: the survival rate of less than 12 month was considered low (Y = 1, totally 29 cases); the survival rate of more than 12 months was considered as a positive result (Y = 0, totally 195 cases). The censored data for the period of monitoring of less than 12 months were excluded from the analysis.

Data were collected and analyzed using MedCalc version 12.3 statistical software (MedCalc Software Inc, Broekstraat, Belgium) and STATISTICA Neural Networks version 4.0 C (StatSoft Inc., 1999).

39 factors were taken for input characteristics: gender, age, height, weight, body mass index (BMI), BMI (categorized index), localization of the tumor and its clinical form (lung, lobes of the lung, central/peripheral cancer), neoplasm size, neoplasm size (categorized index), "T" criterion, "N" criterion, stage of disease, histological and morphological form of tumor differentiation, presence of tumor necrosis, visceral pleura infiltration, volume of conducted surgical measures, volume of lymph dissection, fact of intra pericardial lung vasoligation, conducting of adjuvant radiotherapy and chemotherapy, detection of lung cancer on prophylactic examination, Ki-67 expression, Ki-67 expression (categorized index), CD31/CD34 expression, Her2-neu expression, EGFR expression, p53 expression, E-cadherin expression, pan-cytokeratin expression.

To prevent the re-education and to examine the quality of forecasting model all cases (using a random number generator) were divided into 3 sets: instructive (144 cases used to educate the model), testing (30 cases used to control the re-education of the model) and a confirming set (30 cases-used to assess the mistakes of model generalization).

3. Results

The classification model on the full set (39 factors) of explanatory variables was built. The model was adequate: area under the ROC (Receiver Operating Characteristic) curve [12]; AUC = 0.82 ± 0.05. On the training set the model sensitivity was 94.4% (95% CI 78.1% - 100%) specificity of the model-91.3% (95% CI 85.7% - 95.6%). However, the prognostic characteristics on the test set dramatically decreased ($p < 0.05$): the model sensitivity was 28.6% (95% CI 1.0% - 73.2%), specificity of the model-67.4% (95% CI 52.4% - 80.8%). This reduction in prognostic model characteristics can be attributed to the redundancy of factors.

To reveal factors most associated with the risk of low patient survival rate in the early stage of NSCLC. Selection of the most important characteristics based on Genetic Algorithm (GA) input selection [13]. Two sets of explanatory variables were allocated as a result of the analysis: Model 1 (the patient's BMI, stage of disease, histological form of tumor, volume of conducted surgical measures), Model 2 (the patient's BMI, volume of conducted lymph dissection, EGFR expression).

The forecasting model of the risk of low patient survival rate in the early stage of NSCLC was built on the marked set of factor signs in the Model 1. Its sensitivity on the training set was 77.8% (95% CI 54.6% - 94.2%), specificity—72.2% (95% CI 64.0% - 79.7%), the model sensitivity on the test set was 57.1% (95% CI 14.8% - 93.8%), specificity—55.8% (95% CI 40.5% - 70.6%). The sensitivity and specificity on the training and test sets do not statistically differ ($p = 0.59$ and $p = 0.07$ accordingly) which indicates the adequacy of the developed model.

For revealing the force and direction of the impact of 4 selected explanatory variables a logistic prognostic model was constructed [14]. Values of the coefficients of this model are given in **Table 1**.

Table 1. Coefficients of 4-factor forecasting model of the risk of low patient survival rate.

Factor	The value of forecasting model coefficients, b ± m	Level of significance difference, p	Odds ratio (OR) (95% CI OR)
The patient's BMI	−0.12 ± 0.05	0.03	0.89 (0.80 - 0.99)
Stage of disease	0.04 ± 0.20	0.82	–
Histological form of tumor	−1.00 ± 0.45	0.02	0.36 (0.15 - 0.88)
Type of conducted surgery	1.16 ± 0.46	0.01	3.19 (1.29 - 7.86)

*-statistically significant, $p < 0.05$.

As follows from the analysis (**Table 1**) with the increasing of the patient's BMI the risk of low patient survival rate statistically significant ($p = 0.03$) decreases, odds ratio (OR) = 0.89 (95% CI 0.80 - 0.99) for each kg/m^2 index value. The risk of low patient survival rate also decreases ($p = 0.02$) if he has a squamous cell carcinoma, OR = 0.36 (95% CI 0.15 - 0.88) compared with other histological forms of tumor. The connection between the risk of low patient survival rate and the volume of surgical intervention was discovered ($p = 0.01$), OR = 3.19 (95% CI 1.29 - 7.86) for patients who underwent a pulmonectomy compared with patients who underwent an upper bilobectomy.

Thus, based on this forecasting model, the most favorable prognosis was determined in patients with high BMI, squamous cell lung cancer, conducted surgery in the volume of lobectomy. Accordingly, the unfavorable prognosis was determined in patients with low BMI, non-squamous cell lung cancer, conducted surgery in volume of pulmonectomy.

The forecasting model of the risk of low patient survival rate in the early-stage of NSCLC was built on the marked set of factor signs in the Model 2. Its sensitivity on the training set was 66.7% (95% CI 42.2% - 87.1%), specificity—69.8% (95% CI 61.5% - 77.6%). The model sensitivity on the test set was 42.9% (95% CI 6.2% - 85.2%), specificity—67.4% (95% CI 52.4% - 80.8%). The sensitivity and specificity on the training and test sets do not statistically differ ($p = 0.53$ and $p = 0.92$ accordingly) which indicates the adequacy of the developed model.

For revealing the force and direction of the impact of 3 selected factors a logistic forecasting model was constructed [14]. Values of the coefficients of this model are given in **Table 2**.

As follows from the analysis (**Table 2**) with the increasing of the patient's BMI the risk of low patient survival rate statistically significant ($p = 0.01$) decreases; OR = 0.84 (95% CI 0.74 - 0.96) for each kg/m2 index value.

It is found that with the increasing level of EGFR the expression in the primary tumor the risk of low patient survival rate statistically significant increases ($p = 0.04$), OR = 1.39 (95% CI 1.01 - 1.90) for each graduation rate. The risk of low patient survival rate also increases when conducting the lymph dissection in the volume D0 - D1.

That is the high BMI, low level of EGFR expression, and D2 lymph dissection are favorable prognostic factors. Accordingly, the low BMI, high EGFR expression, and D0 - D1 lymph dissection are unfavorable factors.

Comparison of ROC curves test has been used to compare the prognostic characteristics of the models Model 1 and Model 2 for the prediction of the risk of low patient survival rate in the early-stage of NSCLC. **Figure 1** shows the ROC-curves of the models.

The area under the ROC-curve for Model 1: AUC = 0.72 ± 0.05 statistically significant ($p < 0.001$) differs from 0.5 and indicating the importance of selected variables. The area under the ROC-curve for Model 2: AUC = 0.70 ± 0.05 statistically significant ($p < 0.001$) differs from 0.5 and indicating the importance of selected variables too. There is no significant difference between two AUC ($p = 0.79$).

Therefore, the conducted analysis shows that the risk of low patient survival rate with the early-stage of NSCLC can obtain adequate prediction based on the analysis of patient's BMI, histological structure of the tumor, volume of conducted surgery or patient's BMI, volume of conducted lymph dissection, and the level of EGFR expression.

In both models the patient's BMI is an important prognostic parameter. Moreover, the survival rate worsens with a decrease of this parameter and patients with low BMI have unfavorable prognosis. Except BMI, the histological structure of tumor has the important prognostic value. In our study the non-squamous form of the tumor was prognostic unfavorable. Perhaps this is due to the fact that this version includes malignant neoplasms of glandular structure, mixt-forms and undifferentiated tumors. Another important factor in prediction of disease outcome in patients with the early-stage of NSCLC is the stage of the disease. This fact is not new but confirms the correct selection of explanatory variables and the proper staging in the performance of the study. It is marked that the prognosis deteriorates for examined patients with increasing stage. The type of conducted operative interference and the volume of executed lymph dissection

Table 2. Coefficients of 3-factor forecasting model of the risk of low patient survival rate.

Factor	The value of forecasting model coefficients, b ± m	Level of significance difference, p	Odds ratio (OR) (95% CI OR)
The patient's BMI	–0.17 ± 0.07	0.01*	0.84 (0.74 - 0.96)
The volume of conducted lymph dissection	–1.05 ± 0.60	0.08	–
EGFR expression	0.33 ± 0.16	0.04*	1.39 (1.01 - 1.90)

*-statistically significant, $p < 0.05$.

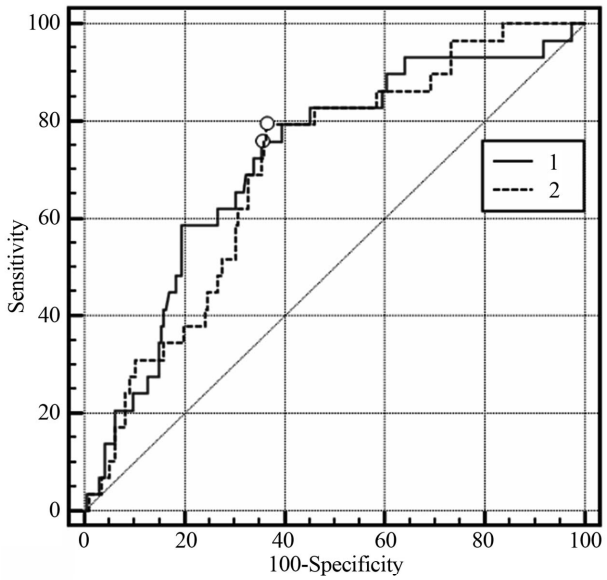

Figure 1. ROC-curves of the models of the risk of low patient survival rate: Model 1 (1), Model 2 (2), –"O" marked optimal values of sensitivity and specificity of the model.

showed the important prognostic value. In patients who underwent the pneumonectomy the deterioration of survival rate was revealed. Perhaps, due to the large spread of tumor at the time of the intervention. At the same time the greater volume of lymph dissection significantly improves the survival rate of patients with the early stage of NSCLC that is possible due to the removal of micro metastases and more correct staging of disease. Of the examined molecular markers the EGFR expression was prognostic significant. This marker indicates the presence of epidermal growth factor on the membrane of tumor cells. The higher number of receptors-the less favorable prognosis of patients examined. This is because of the fact that the work of this receptor is associated with many important processes occurring in the cell, including the increase of proliferation, apoptosis, cell adhesion, increase of metastatic potential of the tumor. Using these prognostic models it is possible to select patients with a poor prognosis for conducting the chemotherapy (PCT).

4. Discussion

A number of studies are devoted to find the prognostic factors [4,8-11]. The analyzed clinical, morphological, genetic factors to predict the survival rate of patients with NSCLC were done. To predict the survival rate Leonardus and coauthors (2010) used a model that included the following clinical factors: sex, age, smoking, function of external breathing, comorbidities, stage, type of resection, histology. It is shown that the forecasting model adequately predicts 1, 2 year survival rate [15]. The following clinical factors were also analyzed in our study: sex, age, height, weight, body mass index (BMI), BMI (categorized index), localization of the tumor and its clinical form (lung, lobes of the lung, central/peripheral cancer), neoplasm size, neoplasm size (categorized index), "T" criterion, "N" criterion, stage of disease. However, only the BMI was prognostic significant. Harpole and coauthors (1995) showed in their study of 1928 patients that in the prognostic correlation of 16 analyzed factors (sex, hemoptysis, cough, chest pain, age, smoking, dyspnea, type of surgical treatment, histology, tumor size, differentiation, vascular invasion, Her-2/neu, p53, Ki-67 expression), the most important are the Her-2/neu status, tumor size more than 3 cm, vascular invasion, p53 status, low differentiation of the tumor [9]. We also investigated the prognostic significance of such molecular factors as histological form and tumor differentiation, Her-2/neu, p53, Ki-67 expression. None of these prognostic factors in the forecasting models is important. Perhaps, it is because of a different set of factors analyzed. In another study 60 morphological factors in 300 patients with advanced NSCLC were examined before the first-line chemotherapy. Prediction and prognostic markers are as follows: general status of patients, extra pulmonary distant metastases, type of chemotherapy, number of leukocytes in the blood, level of albumin CYFRA 21-1, nucleosome, Ca125, Ca15-3 and Ca72-4 [10]. In our study 39 prognostic markers were investigated in 254 patients. It is noted that the independent prognostic factors in the forecasting model are: the BMI, histological type of tumor, stage, type of surgery which had been conducted. The possible alternative combination of factors for predicting the survival rate is as follows: the BMI, volume of lymph dissection, EGFR expression.

Another important factor in the opinion of Park and coauthors (2011) is the presence of necrosis in the primary tumor. It is noted that the tumor necrosis is an in-

dependent prognostic factor. Thus, the five-year survival rate of patients with absence of necrosis was 94.8% and 86.2% in patients with necrosis (p = 0.04). Five-year recurrence-free survival rate in the absence of necrosis was 92.1% and in patients with tumor necrosis–78.9% (p = 0.016) [4]. In our study the tumor invasion in visceral pleura was investigated (except the presence of necrosis in the primary tumor). None of these factors was associated with survival rate of patients.

One of the most important properties of the tumor is proliferation controlled by a group of cyclines. In their study (2001) Dosaka-Akita H. and coauthors noted the different prognostic role of cycline D1 and cycline E. The cycline E correlated with the index of proliferation (measured by Ki-67). The cycline E correlated with the survival rate [16]. According to the data of Lu and coauthors (2004) DAPK methylation and the low IL-10 expression are markers of the negative prognosis for patients [8]. Rubio L. and coauthors (2005) investigated the prognostic role of clinical factors such as factor 8 (microvascular density), VEGF, iNOS, p53, p21. The significant prognostic factors were: tumor size (p = 0.0063), angiogenesis (p = 0.0271) and p21 (p = 0.0478). The authors indicate that the developed prognostic Cox-model allows more careful identifying of the patients with a high risk of disease progression [17].

Among the molecular markers the following markers were studied for constructing the prognostic model: erb-b2, p53, bcl2, Ki-67, Cd-44. The multivariate analysis shows the prognostic role of the following factors: apoptosis (p53), angiogenesis (factor 8), growth factors (erb-b2), adhesion (Cd-44) and the regulation of the cell cycle (recessive gene retinoblastoma) [2,14]. At the same time Hilbe and coauthors (2003) in the study of the prognostic role of growth factors (EGFR or c-erbb-1, c-erbb-2 and c-erbb-3), metastases inhibition parameters (Cd82), markers of proliferation (Ki67, p120) and markers of apoptosis (p53, bcl-2) did not reveal any relation to the survival rate of any marker. However, when combining the factors and survival analysis of patients with high expression of two or three factors (c-erbb-3, p53, and micro vascular density) noted significant deterioration of survival rate [6]. In our research, among the investigated molecular markers were: Ki-67 expression, Ki-67 expression (categorized index), CD31/CD34 expression, Her2-neu expression, EGFR expression, p53 expression, E-kadherinu expression, expression of pan-cytokeratin. However, only the EGFR expression in the Model 2 plays an important prognostic role. The use of the PCR reaction allows analyzing the prognostic significance of various genes. Thus, Raz and coauthors (2008) analyzed the genes Wnt3a, Erbb3, LSK and Rnd3. All the patients were divided into two groups: patients with high and low risk of disease progression. Five-year survival rate had 41% of the patients with the high risk progression and 62% of the patients with the low risk of it [7].

5. Conclusion

In connection with the uncertainty of the "ideal" prediction factors and their combinations, further large studies are necessary to be done [8,14]. Some authors have shown that the use of markers combinations is more beneficial and prognostic than the use of one of them [16].

Therefore, the models developed by us include a number of significant predicting factors that can be used to predict unfavorable survival rate for patients with the early-stage of NSCLC which will help identify patients for further treatment after the operation.

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Abbreviations

ANN—Artificial Neural Network
AUC—Area under the Curve
BMI—Body Mass Index
CI—Confidence Interval
CYFRA—Serum Cytokeratin Fragment
DAPK—Death-Associated Protein Kinase
EGFR—Epidermal Growth Factor Receptor
GA—Genetic Algorithm
IL—Interleukin
iNOS—Inducible Nitric Oxide Synthase
NSCLC—Non-Small Cell Lung Cancer
OR—Odds Ratio
PCR—Polymerase Chain Reaction
PCT—Prognosis for Conducting the Chemotherapy
ROC—Receiver Operating Characteristic
VEGF—Vascular Endothelial Growth Factor