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# Phase Transitions and Cell Ratio Factors in Prediction of Lung Cancer Patients Survival

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**Abstract**
*Objective*: The role of phase transitions (PT) in system "non-small cell lung cancer (LC)—human homeostasis" and cell ratio factors (CRF) (ratio between LC cell population: CC and blood cell subpopulations) for 5-year survival (5YS) after lobectomies/pneumonectomies was analyzed. *Methods*: In trial (1985-2016) the data of consecutive 490 LC patients (LCP) after complete resections R0 (age=56.7±8 years; male - 439, female - 51; tumor diameter: D=4.5±2.1 cm; pneumonectomies - 206, lobectomies - 284, combined procedures with resection of pericardium, atrium, aorta, VCS, carina, diaphragm, esophagus, liver, chest wall, ribs, etc. - 130; squamous cell carcinoma - 308, adenocarcinoma - 147, large cell carcinoma - 35; T1 - 143, T2 - 217, T3 - 107, T4 - 23; N0 - 282, N1 - 115, N2 - 93; G1 - 114, G2 - 140, G3 - 236; early LC: LC till 2 cm in D with N0 - 58, invasive LC - 432) was reviewed. Variables selected for 5YS study were input levels of blood cell subpopulations, TNMG, D. Survival curves were estimated by Kaplan-Meier method. Differences in curves between groups were evaluated using a log-rank test. Neural networks computing, multivariate Cox regression, clustering, discriminant analysis, structural equation modeling, Monte Carlo and bootstrap simulation were used to determine any significant regularity. *Results*: For total of 490 LCP overall life span (LS) was 1824±1304 days and real 5YS reached 62%, 10 years – 50.3%, 20 years – 45.3%. 304 LCP (LS=2597.3±1037 days) lived more than 5 years without LC progressing. 186 LCP (LS=559.8±383.1 days) died because of LC during first 5 years after surgery. 5YS of early LCP was significantly superior (100%) compared with invasive LCP (56.9%) (P=0.000 by log-rank test). 5YS of LCP with N0 was significantly better (78.4%) compared with LCP with N1-2 (39.9%) (P=0.000). Cox modeling displayed that 5YS significantly depended on: PT in terms of synergetics "early-invasive LC", PT N0-N12, CRF (P=0.000-0.004). Neural networks computing, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT "early-invasive LC", (rank=1), PT N0-N12 (2), erythrocytes/CC (3), healthy cells/CC (4), eosinophils/CC (5), lymphocytes/CC (6), monocytes/CC (7), thrombocytes/CC (8), segmented neutrophils/CC (9), leucocytes/CC (10), stab neutrophils/CC (11). Correct prediction of 5YS was 100% by neural networks computing (error=0.000; urea under ROC curve=1.0). *Conclusion*: 5YS of LCP after radical procedures significantly depended on: 1) PT "early-invasive LC"; 2) PT N0-N12; 3) CRF; 4) LC characteristics.

## 1. Introduction

Lung Cancer (LC) is the world global problem. Now a basis of LC prognosis is the modified TNM classification just confirmed on 16$^{th}$ World Congress on Lung Cancer (Denver, the USA, 2015). Unfortunately, this classification considers only characteristics

of a tumor and its metastases, absolutely ignoring a state of patient organism and its prognostic value leaves much to be desired. We analyzed the role of phase transitions (PT) in system "LC—human homeostasis" and cell ratio factors (CRF) (ratio between LC cell population and blood cell subpopulations) for 5-year survival of LC patients (LCP) after complete (R0) lobectomies and pneumonectomies and mediastinal lymph node dissection.

## 2. Patients and Methods

We performed a review of prospectively collected database of European patients undergoing the radical pulmonary resections for LC between 1985 and 2016. 490 consecutive LCP (male – 439, female – 51; age=56.7±8.0 years, tumor size=4.5±2.1 cm) (mean±standard deviation) entered this trial. Patients were not considered eligible if they had N3 lymph node metastasis, stage IV (nonregional lymph nodes metastases, distant metastases, carcinomatous pleurisy, carcinomatosis), previous treatment with chemotherapy, immunotherapy or radiotherapy or if there were two primary tumors at the time of diagnosis. LCP after non-radical procedures and patients, who died postoperatively, were excluded to provide a homogeneous patient group. The preoperative staging protocol included clinical history, physical examination, complete blood count with differentials, biochemistry and electrolyte panel, chest X-rays, röntgenoesophagogastroscopy, computed tomography scan of thorax, abdominal ultrasound, fibrobronchoscopy, electrocardiogram. Computed tomography scan of abdomen, liver and bone radionuclide scan were performed whenever needed. Mediastinoscopy was not used. All LCP were diagnosed with histologically confirmed LC. All had measurable tumor and ECOG performance status 0 or 1. Before surgery each patient was carefully examined by a medical panel composed of thoracic surgeon, chemotherapeutist, radiologist and pneumologist to confirm the stage of disease. All patients signed a written informed consent form approved by the local Institutional Review Board.

Radical procedure was performed through standard thoracotomy. Complete en block anatomical resections (lobectomies, bilobectomies, pneumonectomies) were performed in all patients. All 490 LCP routinely underwent complete systematic hilar and mediastinal lymph node dissection. All mediastinal stations were numbered separately by the surgeon according to the American Joint Committee on Cancer Classification. Complete resection (R0) was defined as removal of the primary tumor and all accessible hilar and mediastinal lymph nodes, with no residual tumor left behind (resection of all macroscopic tumor and resection margins free of tumor at microscopic analysis). Before surgery all patients underwent pulmonary function testing in order to determine the volume of the lungs which can be removed without consequences. For prophylaxis of postoperative respiratory failure LCP were operated, if the preoperative forced expiratory lung volume in 1 second was more 2L and maximum voluntary ventilation was more 35% (especially pneumonectomy). The present analysis was restricted to LCP with complete resected tumors with negative surgical resection margins and with N0-N2 lymph nodes. Surgical complete resection consisted of pneumonectomy in 206, upper lobectomy in 164, lower lobectomy in 87, upper/lower bilobectomy in 25 and middle lobectomy in 8 patients. Among these, 130 LCP underwent combined and extensive radical procedures with the resection of pericardium, atrium, aorta, vena cava superior, vena azygos, carina, trachea, diaphragm, esophagus, liver, chest wall, ribs, etc. All LCP were postoperatively staged according to the TNMG-classification. Histological examination showed squamous cell LC in 308, adenocarcinoma - in 147 and large cell LC - in 35 patients. The pathological TNM stage IA was in 100, IB – in 118, IIA - in 21, IIB – in 117, IIIA - in 111 and IIIB – in 23 patients; the pathological T stage was T1 in 143, T2 - in 217, T3 - in 107, T4 - in 23 cases; the pathological N stage was N0 in 282, N1 - in 115, N2 - in 93 patients. The tumor differentiation was graded as G1 in 114, G2 - in 140, G3 - in 236 cases.

A follow-up examination was, generally, done every 3 month for the first 2 years, every 6 month after that and yearly after 5 years, including a physical examination, a complete blood count, blood chemistry, and chest roentgenography. Zero time was the data of surgical procedures. No one was lost during the follow-up period and we regarded the outcome as death through personal knowledge, physician's reports, autopsy or death certificates. Survival time (days) was measured from the date of surgery until death or the most-recent date of follow-up for surviving patients.

Variables selected for 5-year survival and life span study were the input levels of blood parameters, sex, age, TNMG, cell type, and tumor size. Survival curves were estimated by the Kaplan-Meier method. Differences in curves between groups of LCP were evaluated using a log-rank test. Multivariate proportional hazard Cox regression, structural equation modeling (SEPATH), Monte Carlo simulation, bootstrap simulation and neural networks computing were used to determine any significant dependence [1-7]. Neural networks computing, system, biometric and statistical analyses were conducted using CLASS-MASTER program (Stat Dialog, Inc., Moscow, Russia), SANI program (Stat Dialog, Inc., Moscow, Russia), DEDUCTOR program (BaseGroup Labs, Inc., Riazan, Russia), SPSS (SPSS Inc., Chicago, IL, USA), STATISTICA and STATISTICA Neural Networks program (Stat Soft, Inc., Tulsa, OK, USA), MATHCAD (MathSoft, Inc., Needham, MA, USA), SIMSTAT (Provalis Research, Inc., Montreal, QC, Canada). All tests were considered significant if the resulting P value was less than 0.05.

## 3. Results

For the entire sample of 490 patients overall life span (LS) was 1824±1304 days (mean ±standard deviation) (95% CI,

1708-1940; median=1879). General real 5 year survival reached 62%, 10-year survival – 50.3%, 20-year survival – 45.3%. 282 LCP (57.6%) were alive till now, 304 LCP (62%) lived more than 5 years (LS=2597.3±1037 days) without any features of LC progressing. 186 LCP (38%) died because of relapse and generalization of LC during the first 5 years after surgery (LS=559.8±383.1 days) (Figure 1).

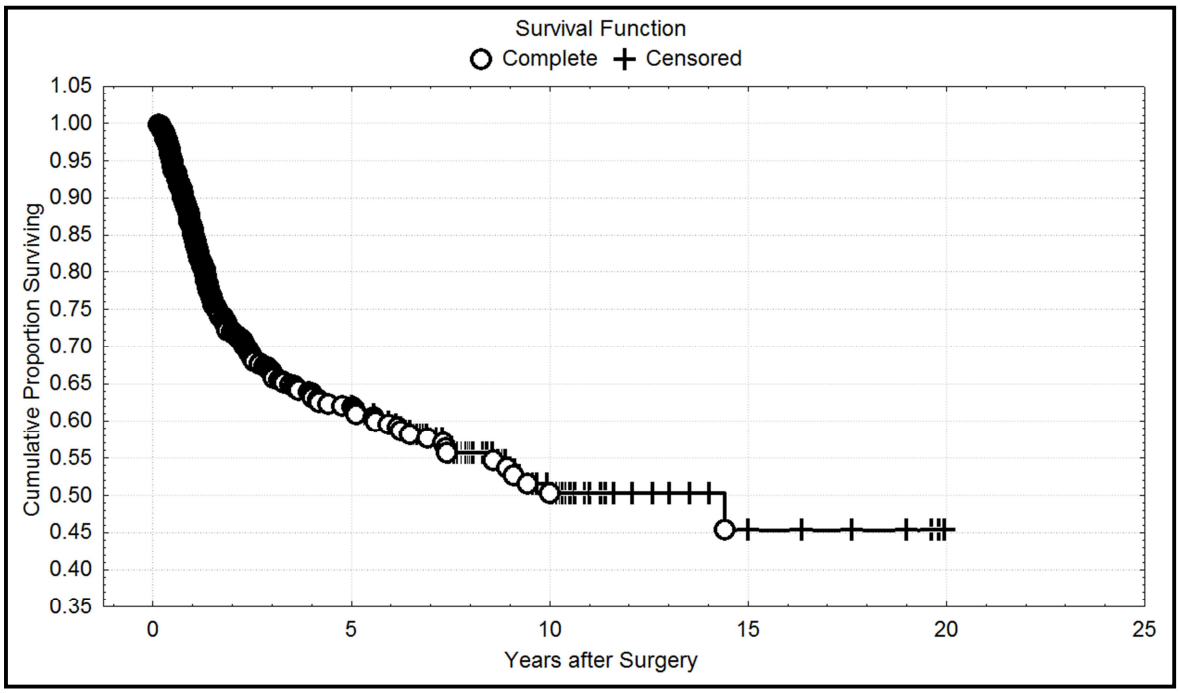


***Figure 1.*** *General cumulative survival of LCP with stage T1-4N0-2M0, n=490 after radical procedures: 5-year survival - 62%, 10-year survival – 50.3%, 20-year survival – 45.3%.*

It is necessary to pay attention to the two very important prognostic phenomenas. First, we found 100% 5-year survival for LCP with early cancer (T1N0, n=58) (LS=2542±1046.4 days) versus 56.9% for other LCP (n=432) (LS=1727.4±1306.5 days) after lobectomies and pneumonectomies (P=0.000 by log-rank test) (Figure 2). Early lung cancer was defined, based on the final histopathologic report of the resection specimen, as tumor limited up to 2 cm in diameter without any lymph node metastasis [8]. Correspondingly, the overall 10-year survival for LCP with the early cancer was 78.4% and was significantly better compared to 46.6% for other patients.

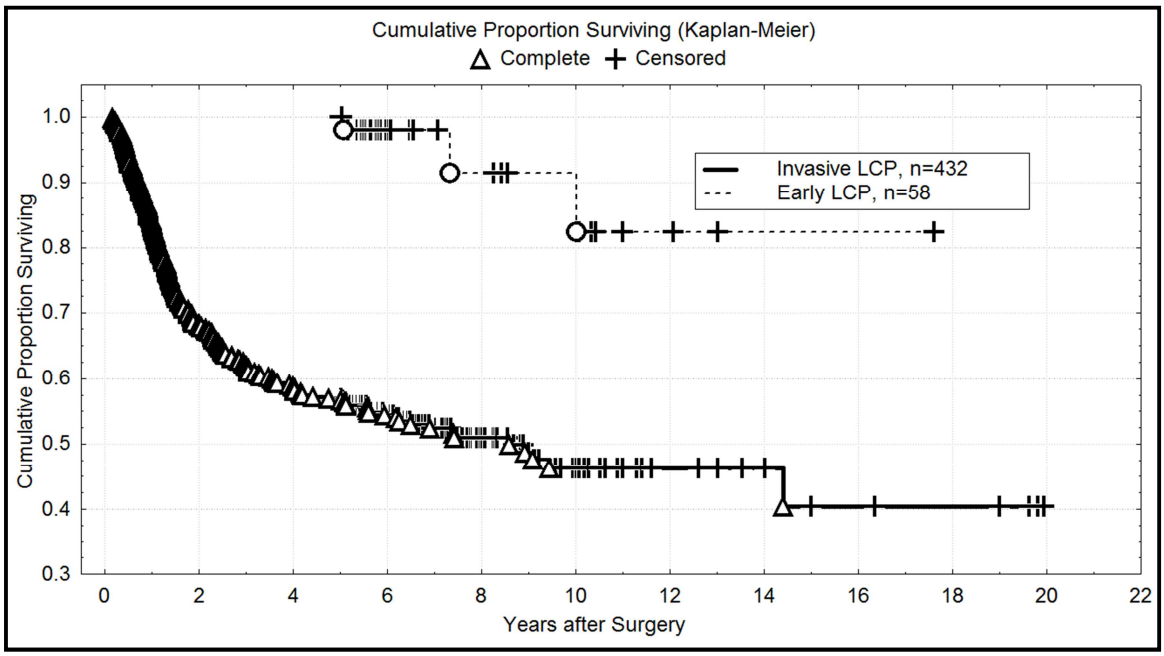


***Figure 2.*** *5-year survival of LCP with early cancer (100%) (n=58) was significantly better compared with invasive cancer (56.9%) (n=432) (P=0.000 by log-rank test).*

Second, we observed excellent 5-year survival of LCP with N0 (78.4%, n=282) (LS=2209.3±1293.1 days) as compared with 5-year survival of LCP with N1-2 (39.9%, n=208) (LS=1301.3±1128.1 days) after radical procedures (P=0.000 by log-rank test) (Figure 3). Accordingly, the overall 10-year survival for LCP with N0 reached 64.1% and was significantly superior compared to 32.2% for LCP with lymph node metastases. Owing to the relatively high frequency of distant failure after surgical resection of LC with lymph nodal metastases, it has been generally accepted that nodal metastases would be an indicator of systemic metastasis [8, 9]. Consequently, at least two separate subsets of patients can be defined from present study: those with N0 status (n=282) and those with N1-2 involvement (n=208). These factors must be taken into account in system analysis of LCP survival and are particularly cogent when attempting to translate obtained results into patient's treatment strategies.

All parameters were analyzed in a multivariate Cox model. In accordance with this Cox model (global $\chi^2$=131.51; Df=7; P=0.000), the six variables significantly explained survival of LCP after surgery: 1) phase transition "early---invasive LC" (P=0.004); 2) phase transition N0---N12 (P=0.000); 3) cell ratio factor (ratio between blood cell subpopulations and cancer cell population): leucocytes/cancer cells (P=0.000); 4) stab neutrophils/cancer cells (P=0.002); 5) segmented neutrophils/cancer cells (P=0.000); 6) lymphocytes/cancer cells (P=0.002) (Table 1).

***Table 1.*** *Results of multivariate proportional hazard Cox regression modeling in prediction of LCP survival after lobectomies and pneumonectomies (n=490).*

| Variables in the Equation | B | SE | Wald | df | P |
|---|---|---|---|---|---|
| Phase Transition "Early---Invasive LC" | -1.729 | 0.593 | 8.490 | 1 | 0.004* |
| Phase Transition "N0---N1-2" | 0.953 | 0.147 | 41.936 | 1 | 0.000* |
| Leucocytes/Cancer Cells | -1.748 | 0.492 | 12.636 | 1 | 0.000* |
| Stab Neutrophils/Cancer Cells | 1.906 | 0.619 | 9.483 | 1 | 0.002* |
| Segmented Neutrophils/Cancer Cells | 1.806 | 0.493 | 13.413 | 1 | 0.000* |
| Lymphocytes/Cancer Cells | 1.582 | 0.502 | 9.925 | 1 | 0.002* |
| Monocytes/Cancer Cells | 1.130 | 0.637 | 3.145 | 1 | 0.076 |

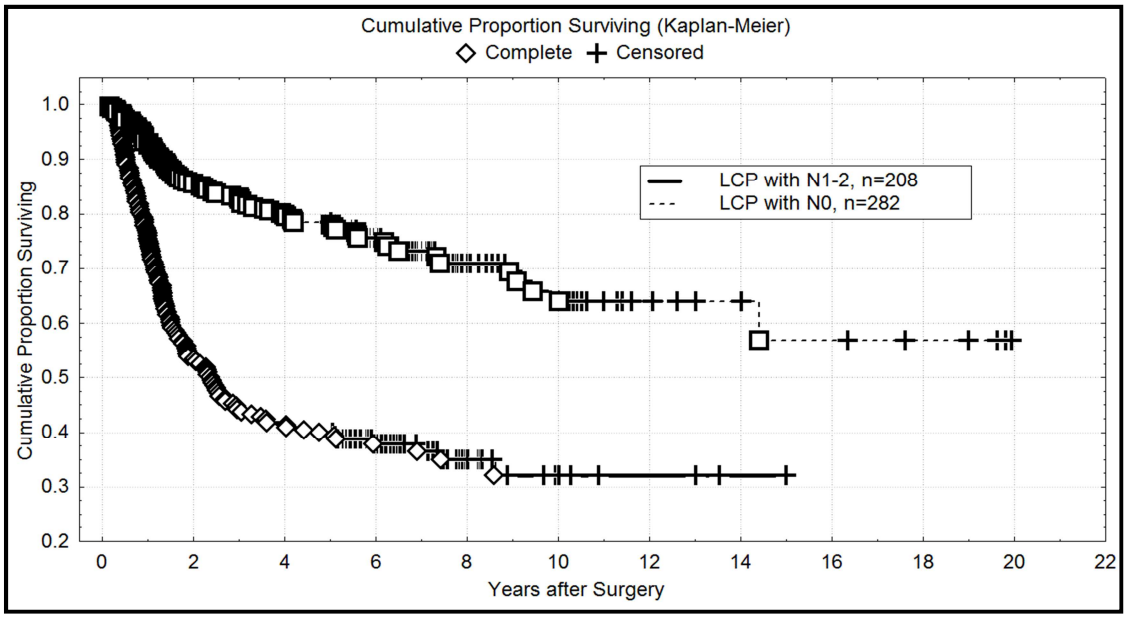


***Figure 3.*** *5-year survival of LCP with N0 (78.4%) (n=282) was significantly better compared with N1-2 metastases (39.9%) (n=208) (P=0.000 by log-rank test).*

For comparative purposes, clinicomorphological variables of LCP (n=490: 304 5-year survivors and 186 losses) were tested by neural networks computing (4-layer perceptron) (Figure 4). Obviously, analyzed data provide significant information about LC prediction. High accuracy of classification – 100% (5-year survivors vs. losses) was achieved in analyzed sample (are under ROC curve=1.0). In other words it remains formally possible that reviled the eleven factors might predate neoplastic generalization: phase transition "N0---N1-2" (rank=1), phase transition "early---invasive LC" (rank=2), cell ratio factor erythrocytes/cancer cells (rank=3), healthy cells/cancer cells (rank=4), eosinophils/cancer cells (rank=5), lymphocytes/cancer cells (rank=6), monocytes/cancer cells (rank=7), thrombocytes/cancer cells (rank=8), segmented neutrophils/cancer cells (rank=9), leucocytes/cancer cells (rank=10) and stab neutrophils/cancer cells (rank=11) (Table 2). Genetic algorithm selection and bootstrap simulation confirmed significant dependence between 5-year survival of LCP after radical procedures and all recognized variables (Tables 3, 4). Moreover, bootstrap simulation confirmed the paramount value of cell ratio factors and the two very special patient's homeostasis states: patients with early LC and patients with N1-2 metastases.

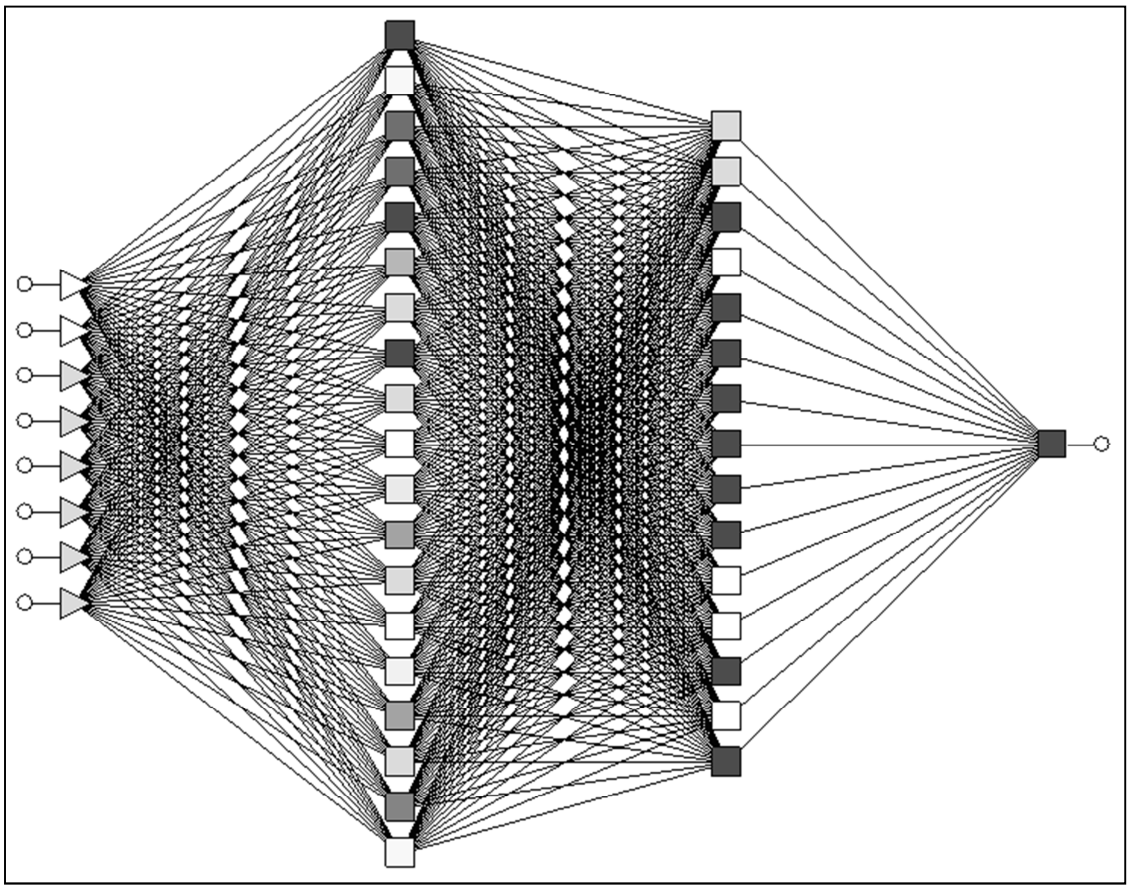

***Figure 4.*** *Configuration of neural networks: 4-layer perceptron.*

***Table 2.*** *Results of neural networks computing in prediction of 5-year survival of LCP after lobectomies and pneumonectomies (n=490: 304 5-year survivors and 186 losses).*

| NN | Factors | Sample n=490 | |
|---|---|---|---|
| | | Rank | Sensitivity |
| 1 | Phase Transition "N0---N1-2" | 1 | 1390.083 |
| 2 | Phase Transition "Early---Invasive LC" | 2 | 1098.398 |
| 3 | Erythrocytes/Cancer Cells | 3 | 589.833 |
| 4 | Healthy Cells/Cancer Cells | 4 | 311.546 |
| 5 | Eosinophils/Cancer Cells | 5 | 302.309 |
| 6 | Lymphocytes/Cancer Cells | 6 | 246.463 |
| 7 | Monocytes/Cancer Cells | 7 | 227.340 |
| 8 | Thrombocytes/Cancer Cells | 8 | 199.914 |
| 9 | Segmented Neutrophils/Cancer Cells | 9 | 194.873 |
| 10 | Leucocytes/Cancer Cells | 10 | 113.597 |
| 11 | Stab Neutrophils/Cancer Cells | 11 | 75.826 |
| | Area under ROC Curve | | 1.0 |
| | Correct Classification Rate (%) | | 100 |

***Table 3.*** *Results of neural networks genetic algorithm selection in prediction of 5-year survival of LCP after lobectomies and pneumonectomies (n=490: 304 5-year survivors and 186 losses).*

| NN | LCP, n=490 Factors | Useful for 5-Year Survival |
|---|---|---|
| 1 | Phase Transition "Early---Invasive LC" | Yes |
| 2 | Phase Transition "N0---N1-2" | Yes |
| 3 | Healthy Cells/Cancer Cells | Yes |
| 4 | Eosinophils/Cancer Cells | Yes |
| 5 | Lymphocytes/Cancer Cells | Yes |
| 6 | Monocytes/Cancer Cells | Yes |
| 7 | Thrombocytes/Cancer Cells | Yes |
| 8 | Segmented Neutrophils/Cancer Cells | Yes |

***Table 4.*** *Results of bootstrap simulation in prediction of 5-year survival of LCP after lobectomies and pneumonectomies (n=490: 304 5-year survivors and 186 losses).*

| NN | LCP, n=490 | Number of Samples=3333 | | |
|---|---|---|---|---|
| | Significant Factors | Rank | Kendall'Tau-A | P< |
| 1 | Phase Transition "N0---N1-2" | 1 | -0.188 | 0.000 |
| 2 | Eosinophils/Cancer Cells | 2 | 0.124 | 0.000 |
| 3 | Erythrocytes/Cancer Cells | 3 | 0.123 | 0.000 |
| 4 | Monocytes/Cancer Cells | 4 | 0.122 | 0.000 |
| 5 | Lymphocytes/Cancer Cells | 5 | 0.121 | 0.000 |
| 6 | Healthy Cells/Cancer Cells | 6 | 0.121 | 0.000 |
| 7 | Thrombocytes/Cancer Cells | 7 | 0.094 | 0.01 |
| 8 | Phase Transition "Early---Invasive LC" | 8 | -0.090 | 0.01 |

It is necessary to note a very important law: both transitions of the early cancer into the invasive cancer, as well as the cancer with N0 into the cancer with N1-N2, have the phase character. These results testify by mathematical (Holling-Tenner) and imitating modeling of system "LC—patient homeostasis" in terms of synergetics (Figures 5, 6). This also proves the first results received earlier in the work [10]. Presence of the two phase transitions is evidently shown on Kohonen self-organizing neural networks maps (Figure 7).

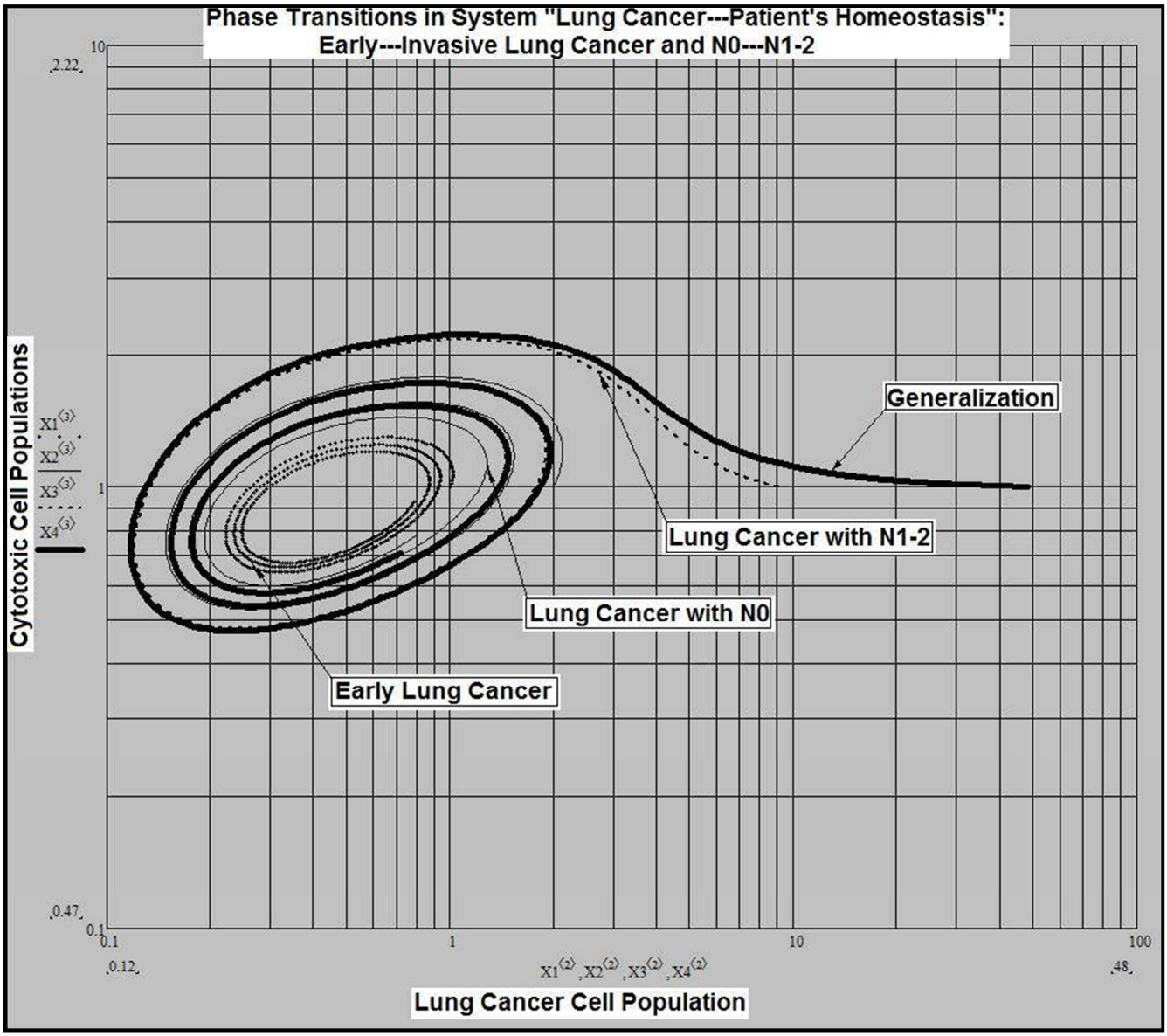


***Figure 5.*** *Results of Holling-Tenner modeling of system "LC—Lymphocytes" in prediction of LCP survival after lobectomies and pneumonectomies (dynamics of early cancer: Lymphocytes/Cancer Cells=1/1; dynamics of cancer with N0: Lymphocytes/Cancer Cells=3/4; dynamics of cancer with N1-2: Lymphocytes/Cancer Cells=2/3; cancer generalization: Lymphocytes/Cancer Cells=1/10).*

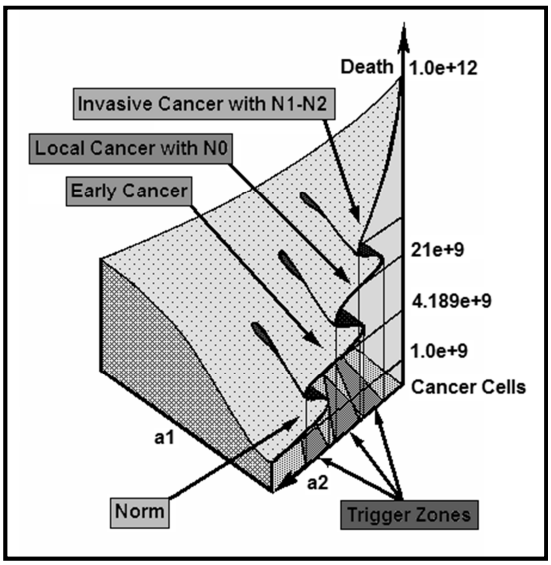


***Figure 6.*** *Presence of the two phase transitions "early cancer—invasive cancer" and "cancer with N0—cancer with N1-2" in terms of synergetics.*

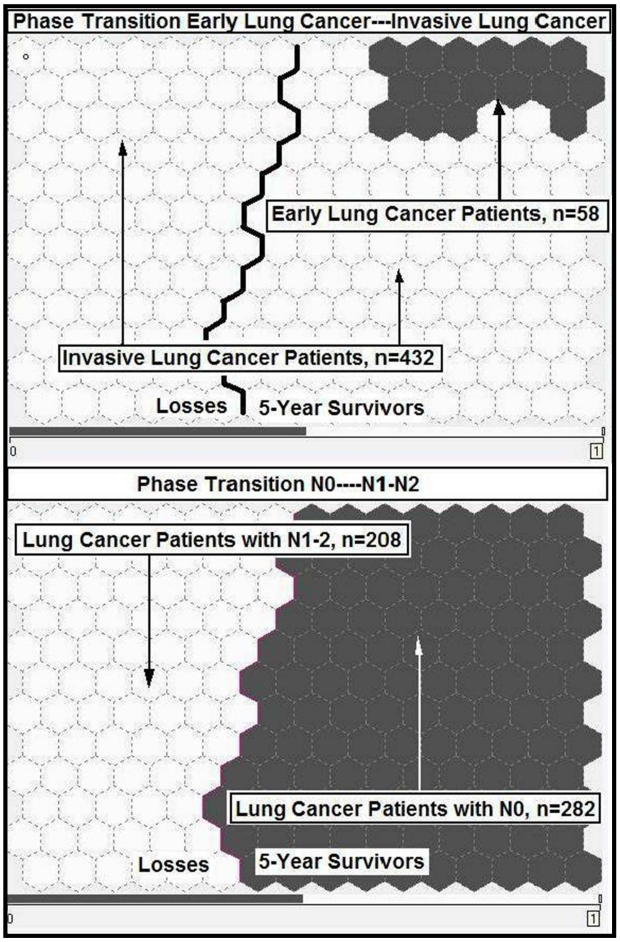


***Figure 7.*** *Results of Kohonen self-organizing neural networks computing in prediction of LCP survival after lobectomies/pneumonectomies (n=490). The black curve line stand for 5-year survivors above and for losses below. Top figure: the area under the dark-color shadow stand for early LCP and the area under the weak-colored shadow stand for invasive LCP. Bottom figure: the area under the dark-color shadow stand for LCP with N0 and the area under the weak-colored shadow stand for LCP with N1-2.*

All of these differences and discrepancies were further investigated by structural equation modeling (SEPATH) as well as Monte Carlo simulation. From the data, summarized in Figure 8 it could be recognized that the four clusters significantly predicted 5-year survival and life span of LCP after complete pulmonary resections: 1) phase transition "early LC—invasive LC" (P=0.002); 2) phase transition "LC with N0—LC with N1-2" (P=0.000); 3) cell ratio factors (P=0.000); 4) LC characteristics (P=0.000) (Figure 8). It is necessary to pay attention, that both phase transitions strictly depend on cell ratio factors (P=0.000) and LC characteristics (P=0.000).

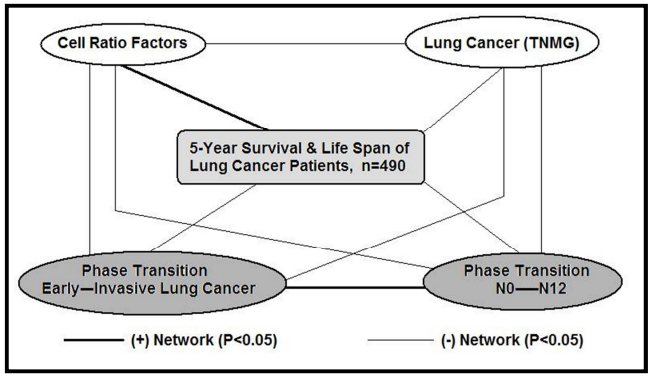


***Figure 8.*** *Significant networks between LCP (n=490) survival, cancer characteristics, cell ratio factors, phase transition "early cancer—invasive cancer" and phase transition "cancer with N0—cancer with N1-2" (SEPATH network model).*

## 4. Discussion

Precise prognosis and prediction of LC is a global problem. On the one hand, modern TNM-classification is based only on cancer characteristics and does not take into account at all the features of extremely complex alive supersystem – the patient's homeostasis. Therefore the prediction of LC is rather inexact and affected by big errors. On the other hand, high-precision prediction is extremely important for exact selection of LCP for adjuvant treatment which is rather toxic and very expensive.

The importance must be stressed of using complex system analysis, artificial intelligence (neural networks computing), simulation modeling and statistical methods in combination, because the different approaches yield complementary pieces of prognostic information. Not stopping in details on these supermodern technologies because of the journal limit rules, great advantage of the artificial intelligence methods is the opportunity to find out hidden interrelations which cannot be calculated by analytical and system methods. Meanwhile, huge merit of simulation modeling is the identification of dynamics of any supersystem, including alive supersystem like human homeostasis, on the hole in time [1-7, 10].

As one regards the early LC, everything becomes quite clear, because for these patients only radical surgery is absolutely sufficient. 5-year survival of patients with early LC after lobectomies reaches 100% and there is no necessity in

adjuvant treatment. From this follows the paramount importance of screening and early detection of LC.

The situation becomes complicated at once if we have local advanced LC and, unfortunately, such patients make up the majority. Without radical procedures these LCP usually perish in several months in spite of the current achievements in chemotherapy, radiotherapy, immunotherapy and gene therapy. Only very skilled surgeons are capable to perform such combined operation adequately. In case of success 25-58% of patients with locally advanced LC live 5 and more years [11, 12].

The most widely accepted treatment strategy for lymph node metastasis is the subsequent initiation of multimodality treatment, including surgery, adjuvant/neoadjuvant chemotherapy or chemoradiation [13-15]. Apparently from present research we have here the two qualitatively various states of a patient's homeostasis. LC with N0 is the local oncopathology and a panacea is the complete lobectomy or pneumonectomy. Lymph node metastasis is a chain reaction or phase transition in terms of synergetics and the disease gets the system character. Therefore this state should be treated by the methods influencing on whole organism after operation: chemotherapy and immunotherapy. At that radical surgical removal of LC and lymph node metastasis plays a paramount role again, allowing to decrease sharply the number of cancer cell population in patient' organism and to warn possible deadly complications (e.g., profuse hemorrhage). Theoretically chemoimmunotherapy is the most effective when used in patients with a relatively low residual malignant cell population (approximately 1 billion cancer cells per patient) in terms of hidden micrometastasis [10]. This is typical clinical situation for LCP with N1-2 after complete pulmonary resections. In the given situation high-precision prediction of LCP survival after surgery, which allows to select concrete patients for adjuvant treatment and to cut huge financial expenses, has a great value.

In conclusion, 5-year survival and life span of LCP after radical lobectomies and pneumonectomies significantly depended on: 1) phase transition "early---invasive LC"; 2) phase transition N0---N12; 3) cell ratio factors; 4) LC characteristics.

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