Lung Cancer: Optimal Treatment Strategies

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Abstract: *Objective*: Search of best treatment plan for non-small lung cancer (LC) patients (LCP) was realized.

Methods: In trial (1985-2008) the data of consecutive 535 LCP after complete resections (R0) (age = 57.3 ± 8.2 years; male-482, female-53; tumor diameter: D = 4.7 ± 2.2 cm; pneumonectomies-222, lobectomies-313, combined procedures with resection of pericardium, atrium, aorta, VCS, carina, diaphragm, ribs-155; only surgery-S-316, adjuvant chemoimmunoradiotherapy-AT-117: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy, postoperative radiotherapy 45-50Gy-RT-102; squamous-341, adenocarcinoma-153, large cell-41; stage IA-105, IB-130, IIA-21, IIB-122, IIIA-116, IIIB-41; T1-150, T2-230, T3-114, T4-41; N0-310, N1-118, N2-107; G1-126, G2-152, G3-257) were reviewed. Variables selected for 5-year survival (5YS) study were input levels of blood, biochemic and hemostatic factors, sex, age, 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, Cox regression, clustering, structural equation modeling, Monte Carlo and bootstrap simulation were used to determine any significant regularity.

Results: For total of 535 LCP overall life span (LS) was 1723.3 ± 1294.9 days and cumulative 5YS reached 63.6%, 10 years – 52.8%. 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 LCP with N1-2 was superior significantly after AT (65.6%) compared with RT (39.5%) (P = 0.0003 by log-rank test) and S (28.3%) (P = 0.000). Cox modeling displayed that 5YS significantly depended on: phase transition (PT)"early-invasive LC", PT N0-N12, AT, age, weight, histology, G, T, D, blood cell subpopulations, cell ratio factors, ESS, prothrombin index, heparin tolerance, recalcification time, bilirubin, (P = 0.000-0.046). Neural networks computing, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT N0-N12 (rank = 1), procedure type, G, T, histology, AT, PT "early-invasive LC", RT, S, sex, ESS, prothrombin index, fibrinogen, Hb, protein, weight, lymphocytes. Correct prediction of 5YS was 99.6% by neural networks computing (error = 0.045; urea under ROC curve = 0.995).

Conclusion: Optimal treatment strategies for LCP are: 1) screening and early detection of LC; 2) availability of experienced surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymphadenectomy for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for LCP with unfavorable prognosis.

INTRODUCTION

Lung Cancer is a global problem of the mankind. In the world 1.5 million new patients with lung cancer are diagnosed each year, from which 85-90% have already died. Approximately 80-85% of these tumors are non-small cell histological type, including adenocarcinomas, squamous cell and large cell carcinomas. Non-small cell lung cancer (LC) is the main cause of death from cancer, and real 5-year survival (5YS) across all stages of the disease is approximately 14% in the USA and 10% in Europe [1, 2]. At the present, radical surgery is generally regarded as the best treatment option, but only approximately 30-50% of tumors are suitable for potentially curative resection depending on quality of diagnostics of LC and aggression and skill of regional thoracic surgeons [1, 3]. Adjuvant chemotherapy has recently become a new standard of care for patients with LC (LCP) after clinical trials showed approximately 5-15% improvement in overall survival for those with higher risk disease, especially for stage II-IIIA [4, 5]. Generally, cancer has immunosuppressive effects on patient's immune circuit [6]. Surgery, chemotherapy and irradiation themselves perturb baseline immune circuit [7]. Clinically, in the total population it is known that poor baseline cytotoxic function of patient immune cells correlates with a higher long-term rate of cancer relapses and generalization after radical procedures [8].

One of the most perspective directions developed to enhance the efficacy of surgery is the combination of chemotherapy, irradiation and immunotherapy or gene therapy which offers the advantage of exposing LC cell population for drugs and immune factors, thus obviating cancer cell-cycle cytotoxic and host-immunoprotective effects [1, 9]. Nevertheless, very few studies have demonstrated convincing clinical results. We developed optimal treatment strategies that incorporate bolus chemotherapy, irradiation and immunotherapy after radical, aggressive en-block surgery and mediastinal lymph node dissection.

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PATIENTS AND METHODS

We performed a review of prospectively collected database of European patients undergoing the complete (R0) pulmonary resections for LC between August 1985 and November 2008. 535 consecutive LCP (male - 482, female - 53; age = 57.3 ± 8.2 years, tumor size = 4.7 ± 2.2 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 any treatment 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.

The initial treatment was started with surgery. Radical procedure was performed through standard thoracotomy. Complete anatomical resections (lobectomies, bilobectomies, pneumonectomies) were performed in all patients. All 535 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 2.0 L 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 nodes. Surgical complete resection consisted of pneumonectomy in 222, upper lobectomy in 179, lower lobectomy in 100, upper/lower bilobectomy in 26 and middle lobectomy in 8 patients. Among these, 155 LCP underwent combined and extensive radical procedures with the resection of pericardium, atrium, aorta, vena cava superior, vena azygos, carina, trachea, diaphragm, liver, chest wall, ribs, etc. All LCP were postoperatively staged according to the TNMG-classification. Histological examination showed squamous cell LC in 341, adenocarcinoma - in 153 and large cell LC - in 41 patients. The pathological TNM stage IA was in 105, IB – in 130, IIA - in 21, IIB – in 122, IIIA - in 116 and IIIB – in 41 patients; the pathological T stage was T1 in 150, T2 - in 230, T3 - in 114, T4 - in 41 cases; the pathological N stage was N0 in 310, N1 - in 118, N2 - in 107 patients. The tumor differentiation was graded as G1 in 126, G2 - in 152, G3 - in 257 cases.

After surgery postoperative chemoimmunoradiotherapy or radiotherapy were accomplished LCP in ECOG performance status 0 or 1.

All patients (535 LCP) were divided between the three protocol treatment: 1) surgery and adjuvant chemoimmunoradiotherapy (117 LCP - group A) (age = 57.7 ± 9.0 years; males - 108, females - 9; tumor size = 5.5 ± 2.5 cm); 2) surgery and postoperative radiotherapy (102 LCP group B) (age = 57.7 ± 7.5 years; males - 91, females - 11; tumor size = 4.7 ± 2.1 cm); 3) surgery alone without any adjuvant treatment (316 LCP – group C) (age = 57.1 ± 8.1 years; males- 283, females - 33; tumor size = 4.3 ± 2.1 cm) – the control group. All patients completed adjuvant therapy (chemoimmunoradiotherapy or radiotherapy).

After complete resections 102 LCP received radiotherapy (^{60}CO; ROKUS, Russia) with a total tumor dose 45-50 Gy starting 2-4 weeks after surgery (group B). Radiation consisted of single daily fractions of 180-200 cGy 5 days weekly. The treatment volume included the ipsilateral hilus, the supraclavicular fossa and the mediastinum from the incisura iugularis to 5-7 cm below the carina. The lower mediastinum was included in cases of primary tumors in the lower lobes. The resected tumor bed was included in all patients. Parallel-opposed AP-PA fields were used. All fields were checked using the treatment planning program COSPO (St.Petersburg, Russia). Doses were specified at middepth for parallel-opposed technique or at the intersection of central axes for oblique technique. No prophylactic cranial irradiation was used.

Adjuvant chemoimmunoradiotherapy consisting of chemotherapy (by CAV till 1998, since 1999 chemotherapy by gemzar and cisplatin), immunotherapy and thoracic radiotherapy was applied to 117 patients (group A). 1 cycle of bolus chemotherapy by CAV was initiated 14 days after surgery and consisted of cyclophosphamid 500 mg/m^2 intravenously (IV) on day 1, doxorubicin 50 mg/m^2 IV on day 1, vincristin 1.4 mg/m^2 IV on day 1. Chemotherapy by gemzar 1250 mg/m2 IV on day 1, 8, 15 and cisplatin 75 mg/m2 on day 1 was initiated on 14 day after surgery. Immunotherapy consisted thymalin or taktivin 20 mg intramuscularly on days 1, 2, 3, 4 and 5. Cycle of immunotherapy was repeated every 21-28 days (4-6 courses). These immunomodulators were produced by Pharmaceutics of Russian Federation (Novosibirsk) and approved by Ministry of Health of Russian Federation. Thymalin and taktivin are preparations from calf thymus, which stimulate proliferation of blood T-cell and B-cell subpopulations and their response [10]. The importance of using immunotherapy must be stressed, because immune dysfunctions of the cell-mediated and humoral response were induced by tumor, surgical trauma, chemotherapy and radiation [1, 7, 8]. Such immune deficiency induced generalization of LC and compromised the long-term therapeutic result. In this sense immunotherapy shielded human organism from side and adverse effects of basic treatment. Chest radiotherapy (45-50 Gy) was administered 7 days after one

cycle chemoimmunotherapy at a daily dose of 1.8-2 Gy. No prophylactic cranial irradiation was used. Two to three weeks after completion of radiotherapy 3-4 courses of chemotherapy by CAV were repeated every 21-28 days. Cycle of chemotherapy by gemzar and cisplatin was repeated every 14 days (4-5 courses). During chemoimmunotherapy antiemetics were administered. Gastrointestinal side effects, particularly nausea and vomiting, were mild, and chemoimmunoradiotherapy was generally well tolerated. Severe leukopenia, neutropenia, anemia and trombocytopenia occurred infrequently. There were no treatment-related deaths.

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 45 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 [11-17]. 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.

RESULTS

For the entire sample of 535 patients overall life span (LS) was 1723.3 ± 1294.9 days (mean ± standard deviation) (95% CI, 1613.3-1833.2; median = 1843). General cumulative 5 year survival reached 63.6%, 10-year survival – 52.8%. 327 LCP (61.1%) were alive till now, 304 LCP (56.8%) lived more than 5 years (LS = 2597.3 ± 1037.0 days) without any features of LC progressing. 186 LCP (34.8%) died because of LC during the first 5 years after surgery (LS = 559.8 ± 383.1 days) (Fig. **1**).

For 117 LCP with N0-2 status in adjuvant chemoimmunoradiotherapy arm (group A), overall LS was 1845.8 ± 1631.6 days (95% CI, 1547.0-2144.5). For 102 LCP with N0-2 status in postoperative radiotherapy arm (group B), overall LS was 1388.8 ± 1110.1 days (95% CI, 1170.8-1606.8) (P = 0.00002 by log-rank for group A). For 316 LCP with N0-2 status in the control (group C), overall LS was 1785.8 ± 1192.2 days (95% CI, 1653.9-1917.8) (P = 0.100 by log-rank for group A and P = 0.00027 for group B). The overall 5-year survival of LCP with N0-2 for group A was 71% and was significantly superior compared to 42.5% for group B (P = 0.00002). The overall 5-year survival for group C was 61.9% (P = 0.100 for group A and P = 0.00027 for group B).

It is necessary to pay attention to the two very important prognostic phenomenas. First, we found 98.3% 5-years survival for LCP with early cancer (T1N0, n = 62) versus 59.1% for other LCP (n = 473) after lobectomies and pneumonectomies (P = 0.000 by log-rank test) (Fig. **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 with N0 [1]. Patients with early LC did not receive adjuvant treatment. Correspondingly, the overall 10-year survival for LCP with the early cancer was 77.1% and was significantly better compared to 48.2% for other patients.

Second, we observed excellent 5-year survival of LCP with N0 (79.3%, n = 310) as compared with 5-year survival of LCP with N1-N2 (42.2%) after radical procedures (P = 0.000 by log-rank test) (Fig. **3**). Accordingly, the overall 10-year survival for LCP with N0 reached 64.9% and was significantly superior compared to 33.7% for LCP with lymph node metastasis. Owing to the relatively high frequency of distant failure after surgical resection of LC with lymph nodal metastasis, it has been generally accepted that nodal metastasis would be an indicator of systemic metastasis [18, 19]. Consequently, at least two separate subsets of patients can be defined from present study: those with N0 status (n = 310) and those with N1-2 involvement (n = 225). 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.

There are no statistical significant differences were found in 5-year survival and life span of LCP with N0 status between groups A (76.8%, n = 52) and B (58.1%, n = 37) (P = 0.070), A and C (78.1%, n = 221) (P = 0.723), but 5-year survival in group C was significantly better than in group B (P = 0.016).

Regarding LCP with N1-2 metastases 5-year survival was much better for group A (65.6%, n = 65) compared to group C (28.3%, n = 95) (P = 0.000) and was superior with respect to group B (37.6%, n = 65) (P = 0.00025) (Fig. **4**). No significant differences were found in 5-year survival of LCP with N1-2 between groups B and C (P = 0.768).

All parameters were analyzed in a multivariate Cox model. In accordance with this Cox model (global χ^2 = 309.44; Df = 32; P = 0.000), the twenty seven variables significantly explained survival of LCP after surgery: LC characteristics, adjuvant chemoimmunoradiotherapy, age, and blood cell subpopulations, hemostasis parameters, cell ratio factor (ratio between blood cell subpopulations and cancer cell population), etc. (Table **1**).

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) (Fig. **5**). To obtain a more exact analysis 45 patients being alive less than 5 years after radical procedures without relapse were excluded from the sample. Multilayer

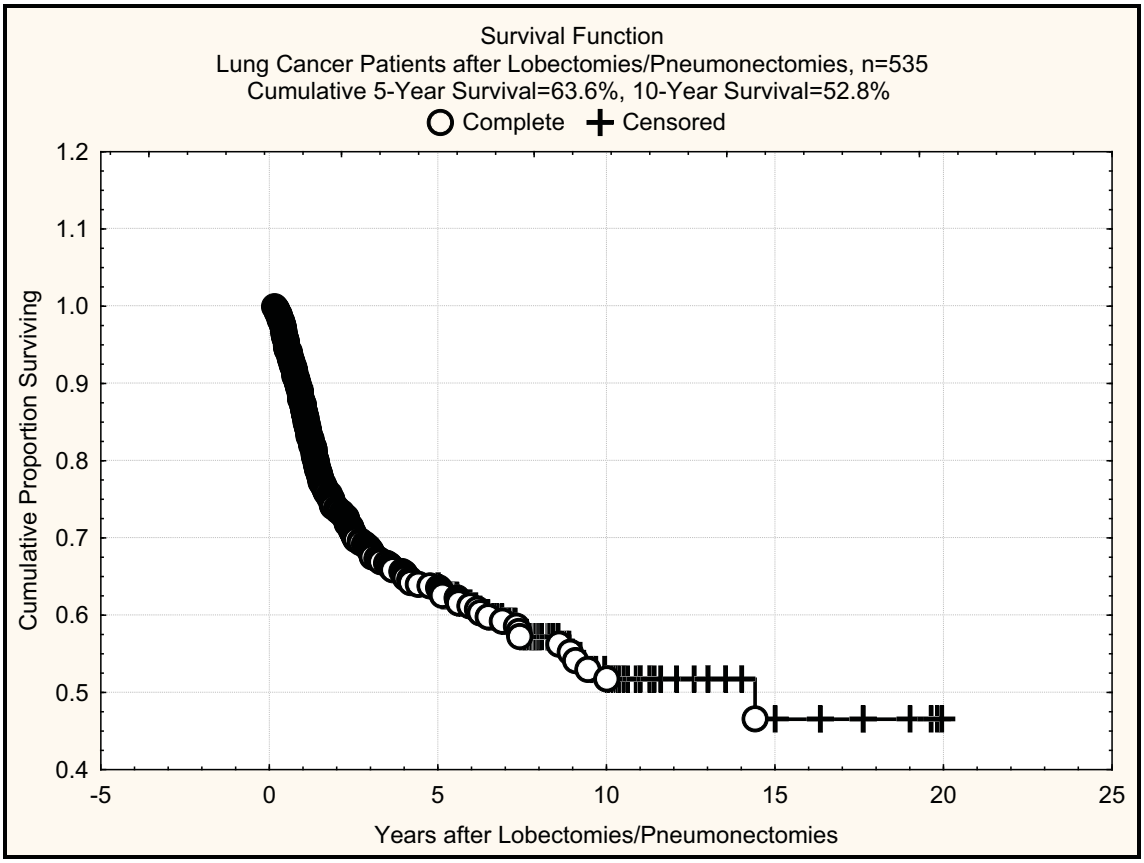

Fig. (1). General cumulative survival of LCP with stage T1-4N0-2M0, n = 535 after radical procedures: cumulative 5-year survival = 63.6%, 10-year survival = 52.8%.

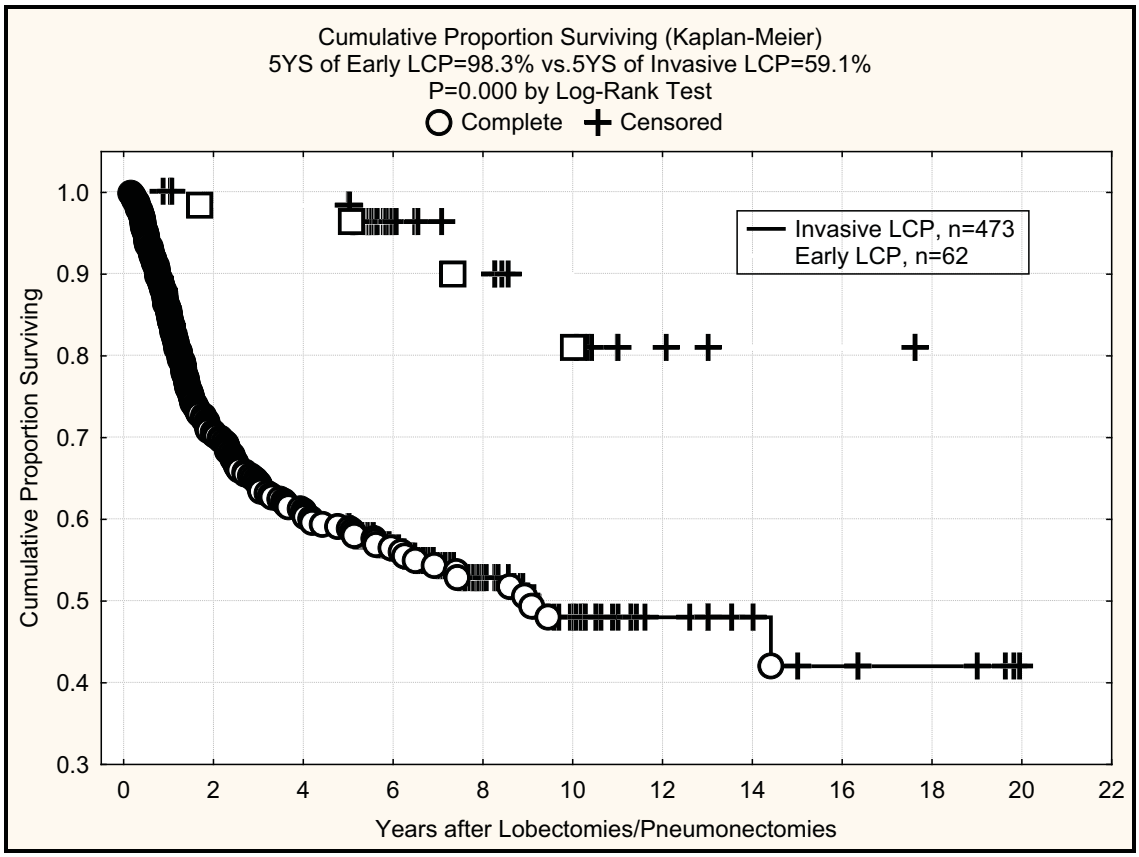

Fig. (2). Survival of LCP with early cancer (n = 62) was significantly better compared with invasive cancer (n = 473) (P = 0.000 by log-rank test).

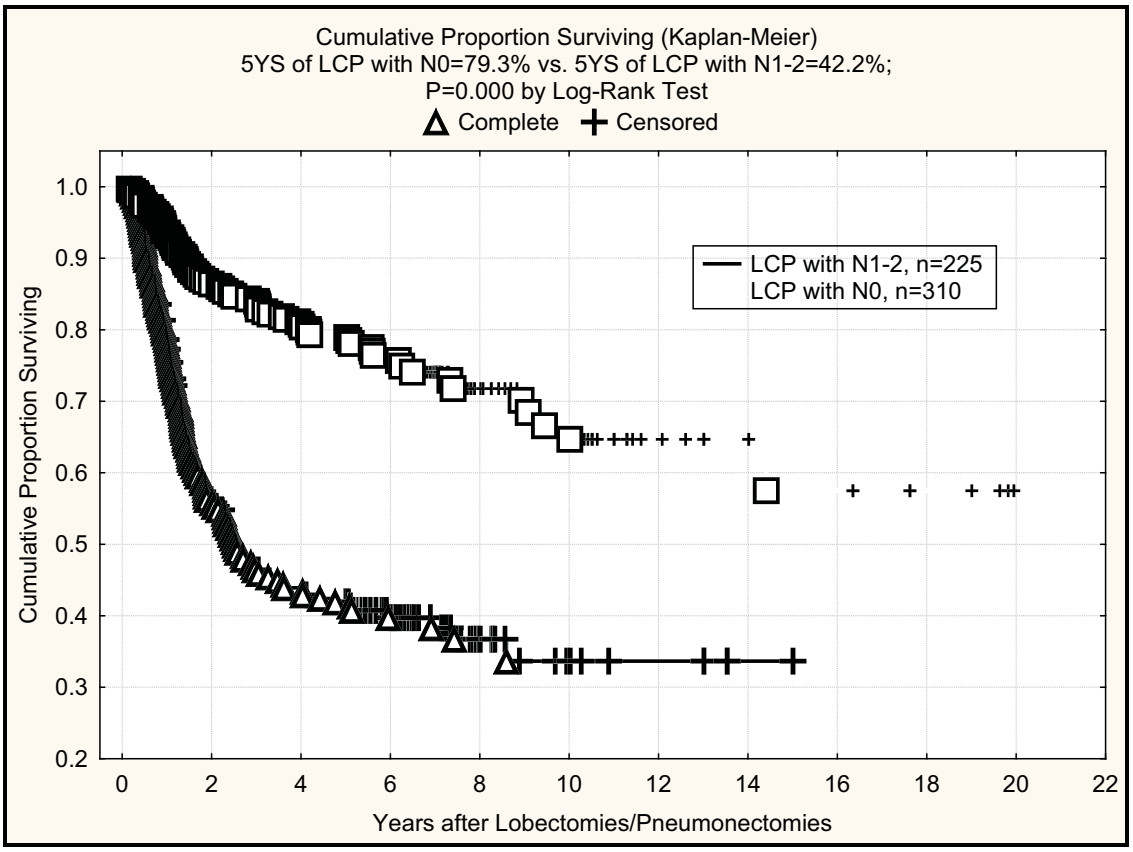

Fig. (3). Survival of LCP with N0 (n = 310) was significantly better compared with N1-N2 metastases (n = 225) (P = 0.000 by log-rank test).

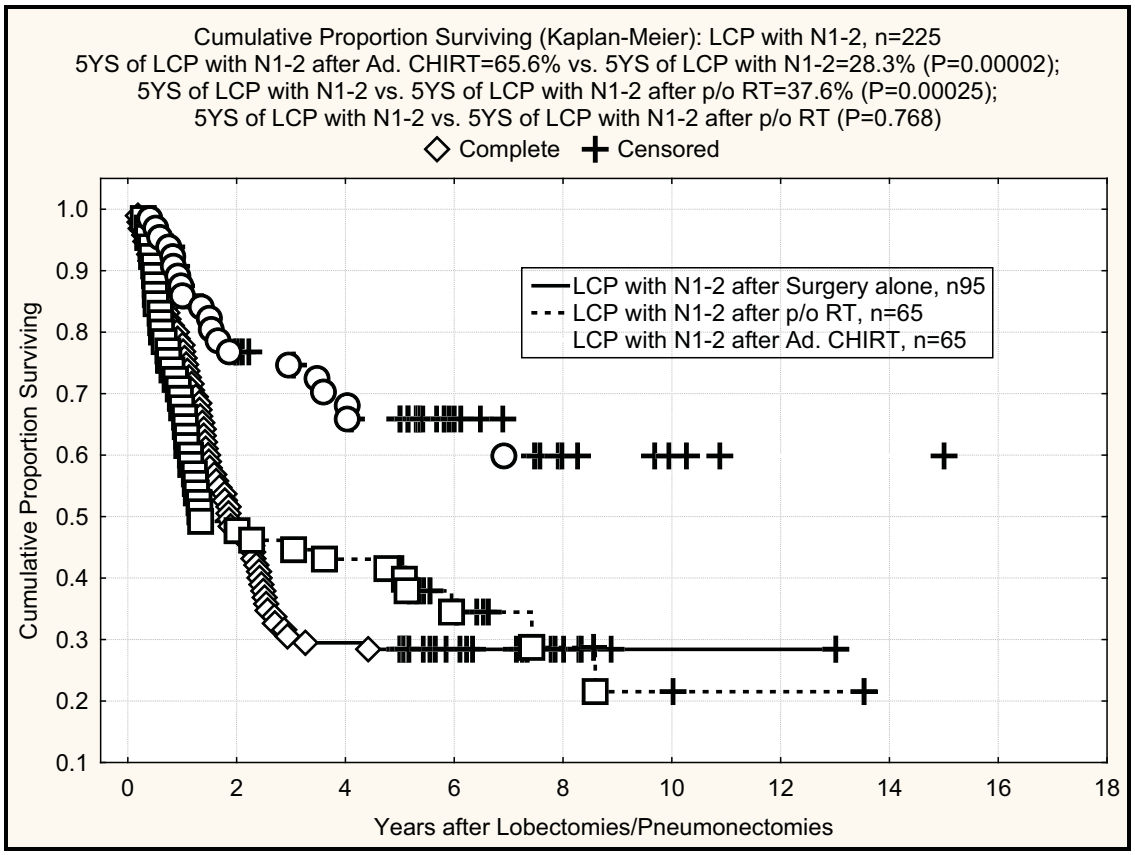

Fig. (4). 5-year survival of LCP with N1-2 after lobectomies and pneumonectomies in group A (adjuvant chemoimmunoradiotherapy: 65.6%, n = 65) was significantly better than in group B (postoperative radiotherapy: 37.6%, n = 65) (P = 0.00025 by log-rank test) and in group C (only surgery: 28.3%, n = 95) (P = 0.000).

Table 1. Results of Multivariate Proportional Hazard Cox Regression Modeling in Prediction of LCP Survival After Lobectomies and Pneumonectomies (n = 535)

Variables in the Equation	B	SE	Wald	df	P
Phase Transition "Early---Invasive LC"	0.691	0.214	10.378	1	0.001
Phase Transition "N0---N1-2"	0.576	0.103	31.153	1	0.000
Tumor Size	0.097	0.047	4.338	1	0.037
T			23.881	3	0.000
T(1)	-1.250	0.299	17.494	1	0.000
T(2)	-1.161	0.244	22.695	1	0.000
T(3)	-0.844	0.233	13.073	1	0.000
G			10.178	2	0.006
G(1)	-0.326	0.132	6.132	1	0.013
G(2)	0.071	0.121	0.340	1	0.560
Histology			10.753	2	0.005
Histology(1)	-0.024	0.117	0.041	1	0.840
Histology(2)	0.678	0.209	10.510	1	0.001
Age	0.021	0.006	11.644	1	0.001
Weight	-0.063	0.017	13.263	1	0.000
Adjuvant Chemoimmunoradiotherapy	-0.687	0.145	22.566	1	0.000
Thrombocytes (abs)	-0.012	0.005	6.933	1	0.008
Thrombocytes (tot)	0.003	0.001	12.261	1	0.000
Leucocytes (tot)	-0.566	0.159	12.680	1	0.000
Stab Neutrophils (tot)	0.911	0.197	21.450	1	0.000
Segmented Neutrophils (tot)	0.539	0.158	11.596	1	0.001
Lymphocytes (tot)	0.554	0.165	11.294	1	0.001
Monocytes (tot)	0.652	0.208	9.791	1	0.002
ESS	-0.010	0.004	8.133	1	0.004
Prothrombin Index	0.030	0.005	36.651	1	0.000
Recalcification Time	-0.004	0.001	6.789	1	0.009
Fibrinogen	0.066	0.035	3.661	1	0.056
Heparin Tolerance	0.003	0.001	34.347	1	0.000
Bilirubin	0.043	0.016	7.203	1	0.007
Leucocytes/Cancer Cells	1.878	0.574	10.697	1	0.001
Stab Neutrophils/Cancer Cells	-3.293	0.735	20.089	1	0.000
Segmented Neutrophils/Cancer Cells	-1.761	0.573	9.463	1	0.002
Lymphocytes/Cancer Cells	-2.104	0.609	11.949	1	0.001
Monocytes/Cancer Cells	-2.087	0.738	7.984	1	0.005
Healthy Cells/Cancer Cells	0.042	0.021	3.976	1	0.046

perceptron was trained by Levenberg-Marquardt method. Obviously, analyzed data provide significant information about LC prediction. High accuracy of classification – 99.6% (5-year survivors *vs* losses) was achieved in analyzed sample (baseline error = 0.045, are under ROC curve = 0.995). In other words it remains formally possible that reviled the seventeen factors might predate neoplastic generalization: N-status (rank = 1), procedure type, G, T, histology, adjuvant chemoimmunoradiotherapy, "early-invasive LC", radiotherapy, surgery along, sex, ESS, prothrombin index, fibrinogen, hemoglobin, protein, weight, lymphocytes (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** and **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 N-1-2 status.

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 "EC-patient homeostasis" in terms of synergetics (Figs. **6**, **7**). This also proves the first results received earlier in the work [1]. Presence of the two phase transitions is evidently shown on Kohonen self-organizing neural networks maps (Fig. **8**).

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 Fig. (**9**) it could be recognized that the nine 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); 5) blood cell circuit (P = 0.014); 6) biochemical homeostasis (P = 0.047); 7) surgery (P = 0.000); 8) adjuvant chemoimmunoradiotherapy (P = 0.000), and 9) postoperative radiotherapy (P = 0.000) (Fig. **9**). It is necessary to pay attention, that both phase transitions strictly depend on blood cell circuit (P = 0.000) and cell ratio factors (P = 0.000).

DISCUSSION

Optimal treatment of LC is a global problem. On the one hand, the lung cancer surgery demands masterly, precise and aggressive surgical technique, especially for LCP with stage T3-4N0-2 and always will remain the privilege of very experienced thoracic surgeons [2, 3]. Actual surgical removal of tumor and lymph node metastases remains basic management of this very aggressive cancer giving the real chance for cure in spite of extensive research over the last 30 years in terms of chemotherapy, radiotherapy, immunotherapy and

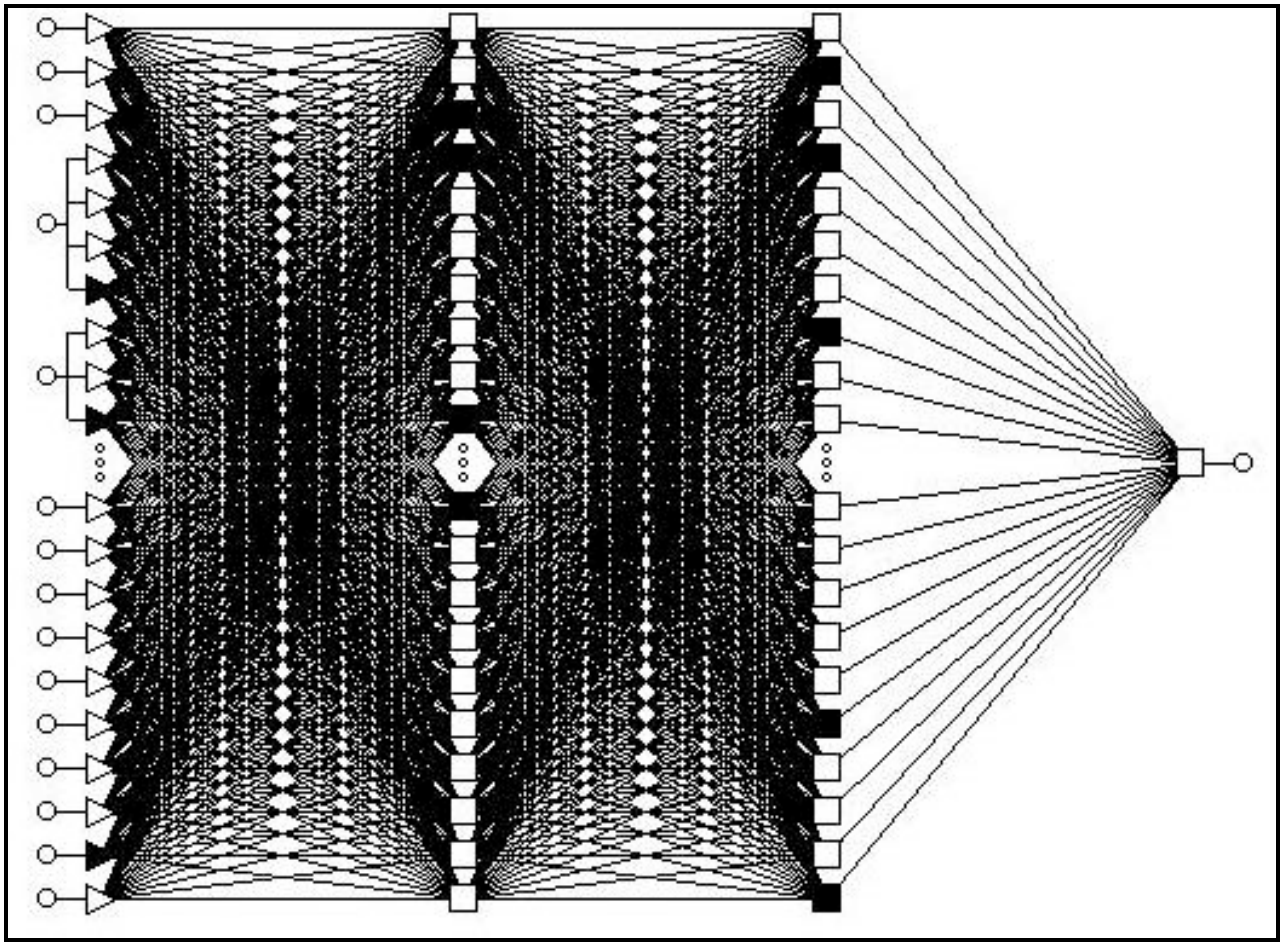

Fig. (5). Configuration of neural networks: 4-layer perceptron.

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	Rank	Sample Error	n = 490 Ratio
1	Phase Transition “N0---N1-2”	1	0.387	8.652
2	Procedure Type	2	0.312	6.908
3	G	3	0.282	6.238
4	T	4	0.210	4.655
5	Histology	5	0.194	4.294
6	Adjuvant Chemoimmunoradiotherapy	6	0.187	4.143
7	Phase Transition “Early---Invasive Cancer”	7	0.178	3.932
8	Postoperative Radiation Therapy	8	0.155	3.429
9	Surgery Along	9	0.150	3.309
10	Gender	10	0.143	3.173
11	ESS	11	0.120	2.655
12	Prothrombin Index	12	0.102	2.259
13	Fibrinogen	13	0.089	1.966
14	Hemoglobin	14	0.085	1.877
15	Protein	15	0.080	1.773
16]17	Weight	16	0.078	1.720
	Lymphocytes (%)	17	0.066	1.46
	Baseline Error	0.045		
	Area under ROC Curve	0.995		
	Correct Classification Rate (%)	99.6		

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 "N0---N1-2"	Yes
2	Phase Transition "Early---Invasive Cancer"	Yes
3	Adjuvant Chemoimmunoradiotherapy	Yes
4	Lymphocytes (tot)	Yes
5	Monocytes (tot)	Yes
6	Eosinophils (tot)	Yes
7	Erythrocytes (tot)	Yes
8	Tumor Size	Yes
9	T	Yes
10	G	Yes
11	Erythrocyte/Cancer Cells	Yes
12	Leucocytes/Cancer Cells	Yes
13	Eosinophils/Cancer Cells	Yes
14	Stab Neutrophils/Cancer Cells	Yes
15	Segmented Neutrophils/Cancer Cells	Yes
16	Healthy Cells/Cancer Cells	Yes
17	Postoperative Radiotherapy	Yes
18	Surgery Along	Yes
19	Gender	Yes
20	Weight	Yes
21	Prothrombin Index	Yes
22	Protein	Yes
23	Procedure Type	Yes
24	ESS	Yes
25	Coagulation Time	Yes
26	Hemorrhage Time	Yes
27	Glucose	Yes

gene therapy [4, 9, 18, 19]. On the other hand, the effectiveness of complete lobectomy and pneumonectomy already reached its limit and leaves much to be desired: the average real 5-year survival rate of radically operated LCP even after combined and extensive procedures is 30-45% and practically is not improved during the past 25-30 years, as the great majority of patients has already LC with stage IIIA-IIIB. And finally, 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 organism. Therefore the prediction of LC is rather inexact and affected by big errors.

Central goal of the present research was to estimate the efficiency of complete lobectomies, bilobectomies and pneumonectomies with adequate lymph node dissection and adjuvant chemoimmunoradiotherapy after radical surgery. 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, 11-17].

Now all LC experts have come to a common opinion, that, first of all, it is necessary to operate LCP at any possibility if, on the one hand, the performance status of the patient is eligible, and, on the other hand, a tumor is probably removable. Certainly, the experience, the art and the aggression of the concrete thoracic surgeon plays the huge role here. If there is a small LC, practically any thoracic surgeon can successfully fulfill the radical operation.

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 90-100% 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 and radiotherapy. Only very skilled surgeons are capable to perform such combined operation adequately. In case of success 25-45% of patients with locally advanced LC live 5 and more years [1, 2].

The most widely accepted treatment strategy for lymph node metastasis is the subsequent initiation of multimodality treatment, including surgery, adjuvant/neoadjuvant chemotherapy or chemoradiation [3-5]. Apparently from present

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	Rank	Number of Samples = 3333	P<
	Significant Factors		Kendall'Tau-A	
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 Cancer"	8	-0.090	0.01
9	Tumor Size	9	-0.088	0.01
10	T	10	-0.087	0.01
11	G	11	-0.071	0.05

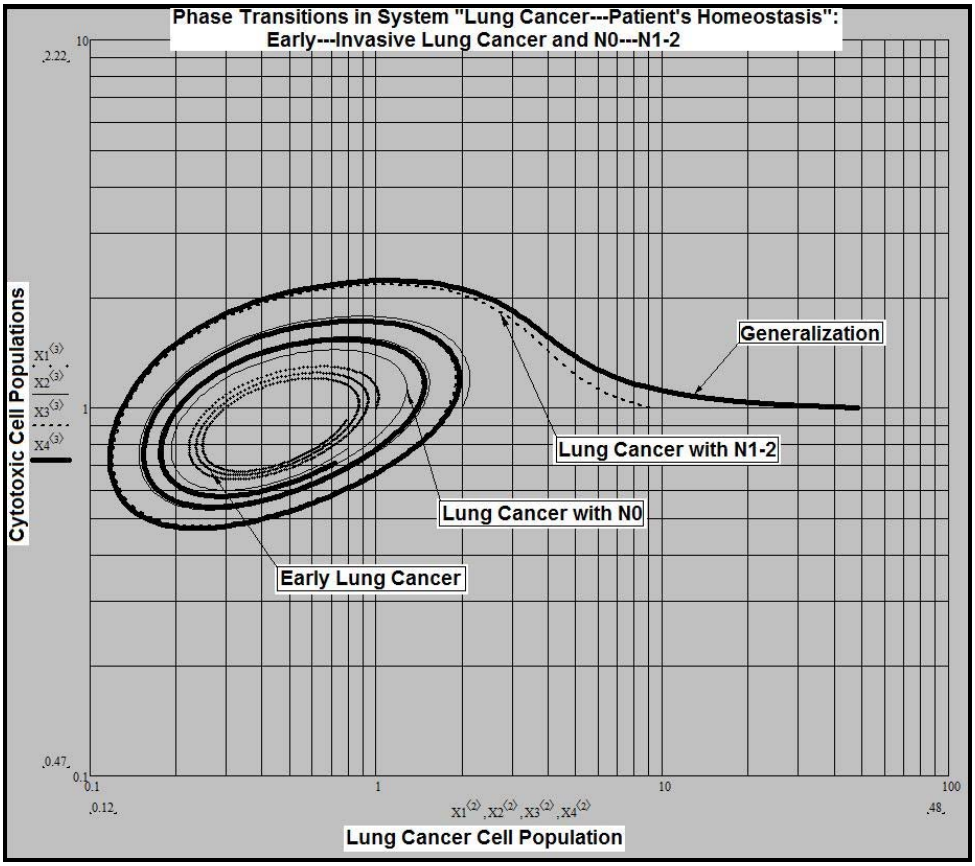

Fig. (6). Results of Holling-Tenner modeling of system "LC-Lymphocytes" in prediction of LCP survival after lobectomies and pneumonectomies (dynamics of early cancer: Lymphocytes/Cancer Cells = 1/1; dynamics of cancer with N0: Lymphocytes/Cancer Cells = 3/4; dynamics of cancer with N1-N2: Lymphocytes/Cancer Cells = 2/3; cancer generalization: Lymphocytes/Cancer Cells = 1/10).

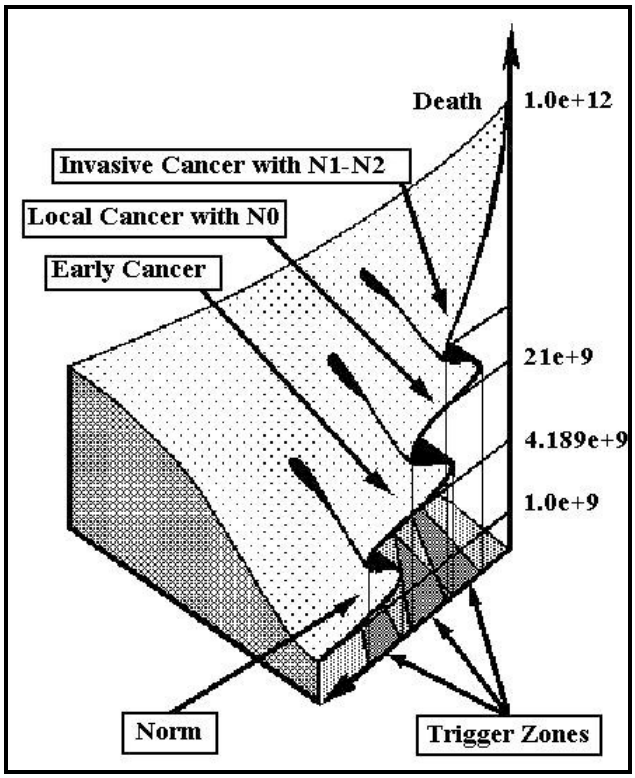

Fig. (7). Presence of the two phase transitions "early cancer-invasive cancer" and "cancer with N0-cancer with N1-2" in terms of synergetics.

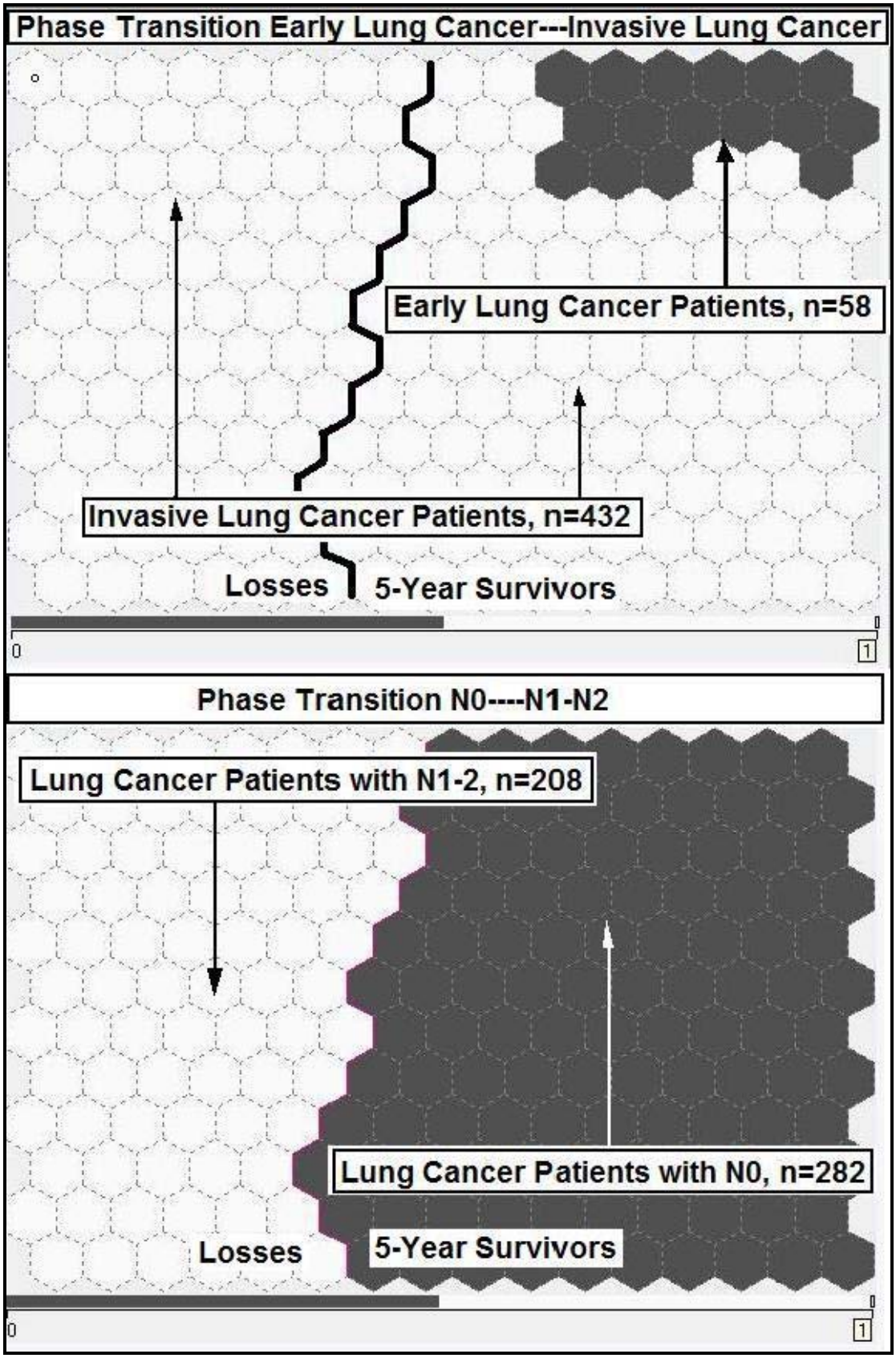

Fig. (8). Results of Kohonen self-organizing neural networks computing in prediction of LCP survival after lobectomies/pneumonectomies (n = 490). The black curve line stand for 5-year survivors above and for losses below. Top figure: the area under the dark-color shadow stand for early LCP and the area 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.

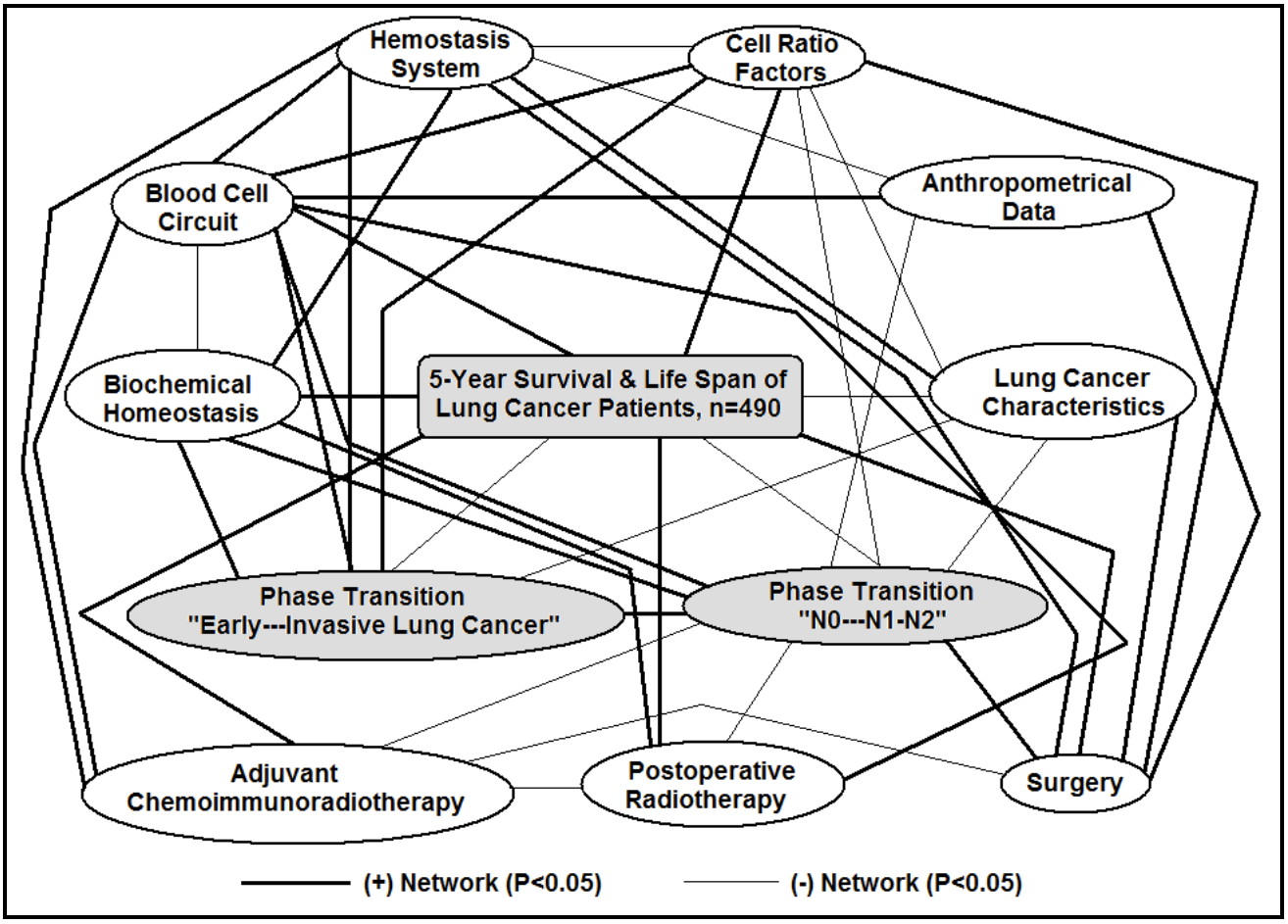

Fig. (9). Significant networks between LCP (n = 490) survival, cancer characteristics, blood cell circuit, cell ratio factors, hemostasis system, biochemic and anthropometric data, phase transition "early cancer-invasive cancer", phase transition "cancer with N0-cancer with N1-2" and treatment protocols (SEPATH network model).

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 [1]. This is typical clinical situation for LCP with N1-2 after complete pulmonary resections. Present research only confirmed this axiom. 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 summary, when adjuvant chemoimmunoradiotherapy is applied to complete lobectomies and pneumonectomies for LC with N1-2, the following benefits should be considered: 1) possibility of total elimination of residual hidden micrometastases; 2) surgery and chemoradiotherapy can result immunosuppressive state, which can be improved by immunotherapy; 3) radical operated LCP with stage IIA-IIIB are thought to be potentially good candidates for adjuvant chemoimmunoradiotherapy as the majority of these patients would be expected to have LC progressing.

Concerning LCP with N0 further investigations will be required to determine efficiency, compatibility and tolerance of new drugs and immunomodulators after surgery. The results of the present research will offer guidance for the design of future studies.

In conclusion, optimal treatment strategies for LCP are: 1) screening and early detection of LC; 2) availability of experienced surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymphadenectomy for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for LCP with unfavorable prognosis.

REFERENCES

[1] Kshivets O. Expert system in diagnosis and prognosis of malignant neoplasms. Dissertion for ScD, Tomsk 1995; p. 486.

[2] Bedrettin Yildizeli, Dartevelle PG, Elie Fadel, *et al*. Results of primary surgery with T4 non-small cell lung cancer during a 25-

year period in single center: the benefit is worth the risk. Ann Thorac Surg 2008; 86: 1065-75.
[3] Robinson LA, Ruckdeschel JC, Wagner H Jr, Stevens CW. Treatment of non-small cell lung cancer-stage IIIA. ACCP evidence-based clinical practice guidelines (2nd ed). Chest 2007; 132: 243-65.
[4] Sedrakyan A, Van Der Meulen J, O'Byrne K, *et al.* Postoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 2004; 128: 414-19.
[5] Kshivets O. Non-small cell lung cancer: the role of chemoimmunoradiotherapy after surgery. J Exp Clin Cancer Res 2001; 20(4): 491-503.
[6] Kshivets O. Early detection and diagnosis of lung cancer and immune circuit. Open Lung Cancer J 2008; 1: 1-12.
[7] Bryan A, Whitson MD, D'Cunha J, *et al.* Thoracoscopic versus thoracotomy approaches to lobectomy: differential impairment of cellular immunity. Ann Thorac Surg 2008; 86: 1735-44.
[8] Kshivets O. Immune cell and humoral circuit in prediction of non-small cell lung cancer patients survival after complete resections. J Tumor Marker Oncol 2001; 16(2): 161-74.
[9] Yano T, Sugio K, Yamazaki K, *et al.* Postoperative adjuvant adoptive immunotherapy with lymph node-LAK cells and IL-2 for pathologic stage I non-small cell lung cancer. Lung Cancer 1999; 26: 143-48.
[10] Morozow VG, Chavinson VC. Isolation, refinement and identification of immunomodulated polypeptide from calf and human thymus. Biochemistry 1981; 9: 1652-59.
[11] Bazykin AD. Mathematical biophysics of cooperating populations. Science: Moscow 1985; p. 181.
[12] Haken H. Information and self-organization. A macroscopic approach to complex systems. Springer: Berlin 2006; p. 240.
[13] Odom-Maryon T. Biostatistical methods in oncology. Cancer management: A multidisciplinary approach. 1st ed. Huntington, NY: PRP Inc. 1996; pp. 788-802.
[14] Mirkin BG. A sequential fitting procedure for linear data analysis models. J Classification 1990; 7: 167-96.
[15] Joreskog KG, Sorbom D. Recent development in structural equation modeling. J Market Res 1982; 19: 404-16.
[16] Bostwick DG, Burke HB. Prediction of individual patient outcome in cancer: comparison of artificial neural networks and Kaplan-Meier methods. Cancer 2001; 91(8): 1643-46.
[17] Husmeier D. The Bayesian evidence scheme for regularizing probability-density estimating neural networks. Neural Comput 2000; 12(11): 2685-17.
[18] Kshivets O. Esophageal cancer: Optimization of management. Open Cardiovasc Thorac Surg J 2008; 1: 1-11.
[19] Kang CH, Ra YJ, Kim YT, *et al.* The impact of multiple metastatic nodal stations on survival in patients with resectable N1 and N2 non-small cell lung cancer. Ann Thorac Surg 2008; 86(4): 1092-97.

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