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Non-small cell lung cancer: 10-year survival after surgery

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Abstract

Objective: 10-Year survival (10YS) after radical surgery for non-small cell lung cancer (LC) patients (LCP) (T1-4N0-2M0) was analyzed.

Methods: We analyzed data of 768 consecutive LCP (age=57.6±8.3 years; tumor size=4.1±2.4 cm) radically operated (R0) and monitored in 1985-2021 (m=660, f=108; upper lobectomies=277, lower lobectomies=177, middle lobectomies=18, bilobectomies=42, pneumonectomies=254, mediastinal lymph node dissection=768; combined procedures with resection of trachea, carina, atrium, aorta, VCS, vena azygos, pericardium, liver, diaphragm, ribs, esophagus=193; only surgery-S=618, adjuvant chemoimmunoradiotherapy-AT=150: CAV/gemzar + cisplatin + thymalin/taktivin + radiotherapy 45-50Gy; T1=320, T2=255, T3=133, T4=60; N0=516, N1=131, N2=121, M0=768; G1=194, G2=243, G3=331; squamous=417, adenocarcinoma=301, large cell=50; early LC=214, invasive LC=554; right LC=412, left LC=356; central=290; peripheral=478. Variables selected for 10YS study were input levels of 45 blood parameters, sex, age, TNMG, cell type, 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 Cox modeling, analysis, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine any significant dependence.

Results: Overall life span (LS) was 2244.9±1750.3 days and cumulative 5-year survival (5YS) reached 72.9%, 10 years – 64.3%, 20 years – 43.1%. 502 LCP lived more than 5 years (LS=3128.7±1536.8 days), 145 LCP – more than 10 years (LS=5068.5±1513.2 days).199 LCP died because of LC (LS=562.7±374.5 days). AT significantly improved 10YS (52.4% vs. 27.7%) (P=0.00002 by log-rank test) only for LCP with N1-2. Cox modeling displayed that 10YS of LCP significantly depended on: phase transition (PT) early-invasive LC in terms of synergetics, PT N0—N12, cell ratio factors (ratio between cancer cells- CC and blood cells subpopulations), G1-3, histology, glucose, AT, blood cell circuit, prothrombin index, heparin tolerance, recalcification time, weight, color index (P=0.000-0.039). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 10YS and PT early-invasive LC (rank=1), thrombocytes/CC (rank=2), PT N0—N12(rank=3), segmented neutrophils/CC (4), healthy cells/CC (5), lymphocytes/CC (6), erythrocytes/CC (7), stick neutrophils/CC (8), eosinophils/CC (9), leucocytes/CC (10), monocytes/CC (11). Correct prediction of 5YS was 100% by neural networks computing (area under ROC curve=1.0; error=0.0).

Conclusions: 10-Year survival of LCP after radical procedures significantly depended on: 1) PT early-invasive cancer; 2) PT N0--N12; 3) cell ratio factors; 4) blood cell circuit; 5) biochemical factors; 6) hemostasis system; 7) AT; 8) LC characteristics; 9) anthropometric data; 10) surgery type. Optimal diagnosis and treatment strategies for LC are: 1) screening and early detection of LC; 2) availability of experienced thoracic surgeons because of complexity of radical

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procedures; 3) aggressive en block surgery and adequate lymph node dissection for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for LCP with unfavorable prognosis.

Keywords: Lung cancer; 10—Year survival; Surgery; Prognosis.

1. Introduction

In the world, lung cancer is the number 1 killer today, despite the astronomical efforts of humankind to fight it. It seems strange that there are no data on 10-year survival in the literature, which is extremely important for optimizing the treatment and diagnostic process. In the world, 2.2 million new patients with lung cancer were diagnosed each year, from which 79-90% 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 21% in the USA and 16% in Europe [1,6]. 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, 4, 5, 23]. 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 [3,4,5]. Generally, cancer has immunosuppressive effects on patient's immune circuit [2,6,11]. 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, check-point inhibitors and host-immunoprotective effects [1,2,9]. Nevertheless, it seems strange that there are no data on 10-year survival of LCP in the literature, which is extremely important for optimizing the treatment and diagnostic process. We developed optimal treatment strategies that incorporate bolus chemotherapy, irradiation and immunotherapy after radical, aggressive en-block surgery and mediastinal lymph node dissection.

2. 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 2021. 768 consecutive LCP (male – 660, female – 108; age=57.6±8.3 years, tumor size=4.1±2.4 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 768 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 254, upper lobectomy in 277, lower lobectomy in 177, upper/lower bilobectomy in 42 and middle lobectomy in 18 patients. Among these, 193 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 417, adenocarcinoma - in 301 and large cell LC - in 50 patients. The pathological TNM stage IA was in 257, IB – in 154, IIA - in 42, IIB – in 130, IIIA - in 133 and IIIB – in 52 patients; the pathological T stage was T1 in 320, T2 - in 255, T3 - in 133, T4 - in 60 cases; the pathological N stage was N0 in 516, N1 - in 131, N2 - in 121 patients. The tumor differentiation was graded as G1 in 194, G2 - in 243, G3 - in 331 cases. Early LC was in 214, invasive LC – in 554; right LC - in 412, left LC – in 356; central LC – in 290; peripheral LC – in 478.

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

All patients (768 LCP) were divided between the two protocol treatment: 1) surgery and adjuvant chemoimmunoradiotherapy (150 LCP – group A); 2) surgery alone without any adjuvant treatment (618 LCP – group B) – the control group. All patients completed adjuvant therapy (chemoimmunoradiotherapy or radiotherapy).

Adjuvant chemoimmunoradiotherapy consisting of chemotherapy (by CAV till 1998, since 1999 chemotherapy by gemzar and cisplatin), immunotherapy and thoracic radiotherapy was applied to 150 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 [13]. 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 [1,2,3,11]. 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 was administered 7 days after one cycle chemoimmunotherapy at a daily dose of 1.8-2 Gy (^{60}CO; ROKUS, Russia) with a total tumor dose 45-50 Gy. 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. 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 10YS and life span study were sex, age, TNM, cell type, 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 and neural networks computing were used to determine any significant dependence [14-18]. 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), STATISTICA and STATISTICA Neural Networks program (Stat Soft, Inc., Tulsa, OK, the USA), DEDUCTOR program (BaseGroup Labs, Inc., Riazan, Russia), SPSS (SPSS Inc., Chicago, IL,

USA), Table Curve3D (Systat Software Inc., San Hose, CA, USA), SIMSTAT2.6 (Provalis Research, Montreal, Canada). All tests were considered significant when the resulting P value was less than 0.05.

3. Results

For the entire sample of 768 patients overall life span (LS) was 2244.9±1750.3 days (mean ±standard deviation). General cumulative 5 year survival reached 72.9%, 10-year survival – 64.3%, 20-year survival – 43.1%. 502 LCP lived more than 5 years (LS=3128.7±1536.8 days) without any features of LC progressing, 145 LCP – more than 10 years after surgery (LS=5068.5±1513.2 days). 199 LCP died because of LC during the first 5 years after surgery (LS=562.7±374.5 days) (Fig. 1).

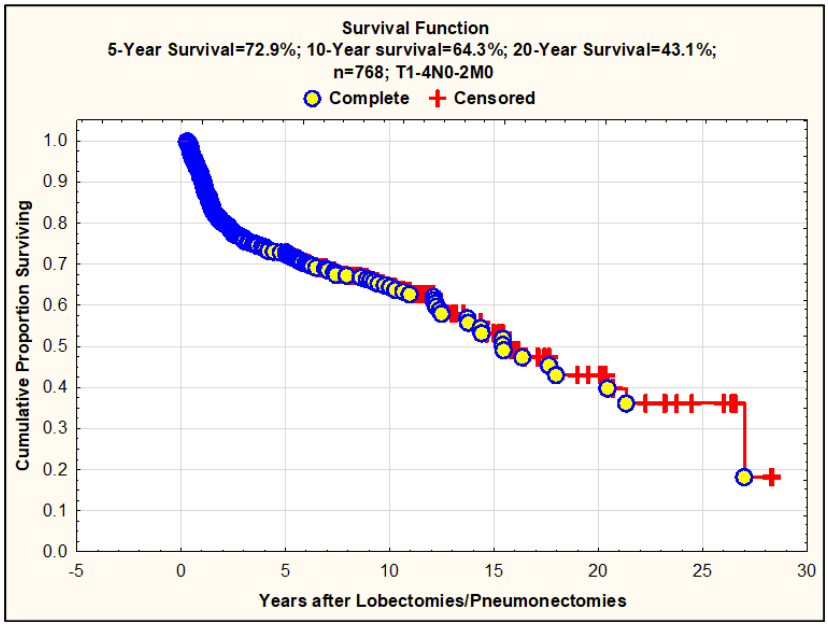

Figure 1 General cumulative survival of LCP with stage T1-4N0-2M0, n=768 after radical procedures: cumulative 10-year survival=64.3%, 20-year survival=43.1%

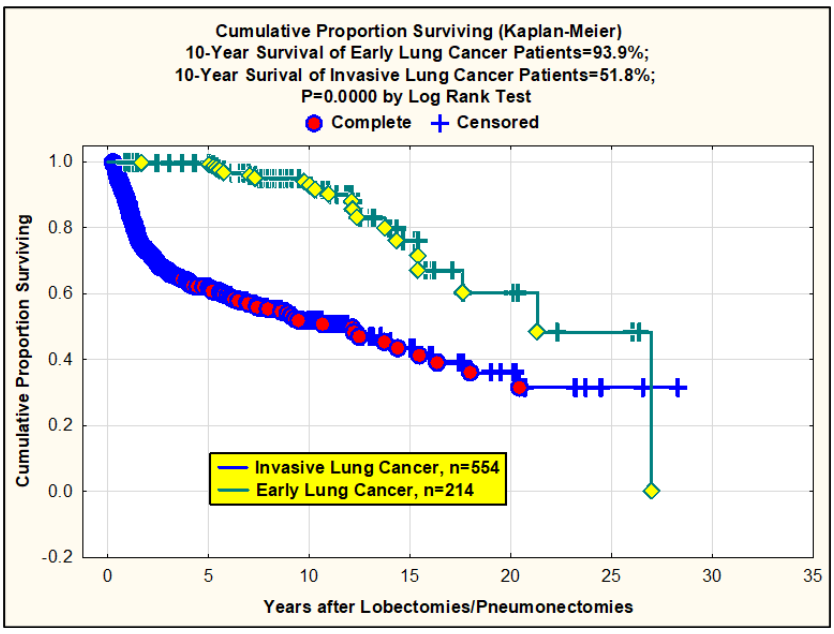

Figure 2 10-year survival of LCP with early cancer 93.9% (n=214) was significantly better compared with invasive cancer 51.8% (n=554) (P=0.0000 by log-rank test)

It is necessary to pay attention on the five very important prognostic phenomenons. First, 93.9% 10-year survival (10YS) for LCP with the early cancer as against 51.8% for the others LCP after surgery (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 [1,24]. Patients with early LC did not receive adjuvant treatment.

Second, good 10YS for LCP with N0 (78.3%) as compared with LCP with N1-2 (10YS was 35.2%) after radical procedures (P=0.000 by log-rank test) (Fig.3).

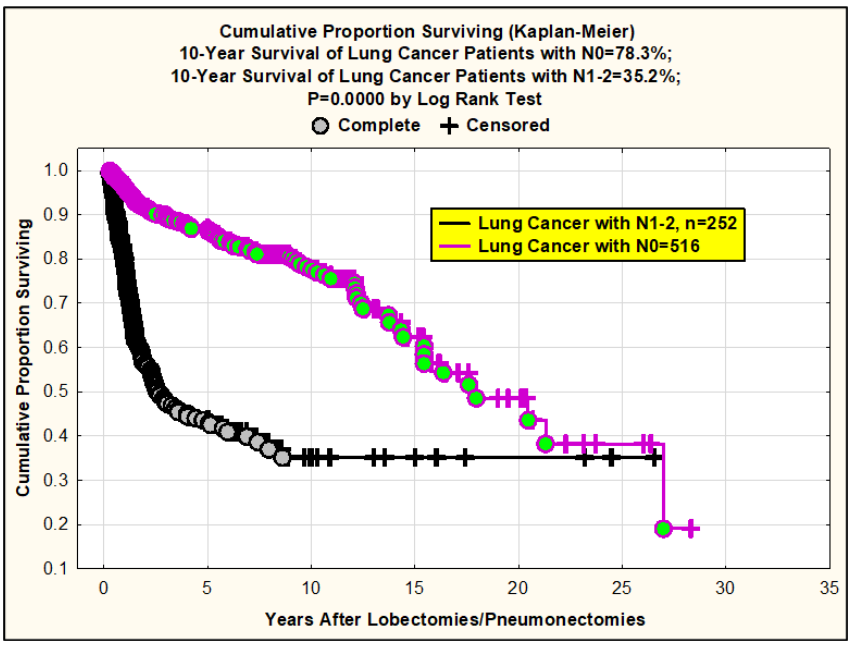

Figure 3 10-year survival of LCP with N0 78.3% (n=516) was significantly better compared with LCP with N1-N2 metastases 35.2% (n=252) (P=0.0000 by log-rank test)

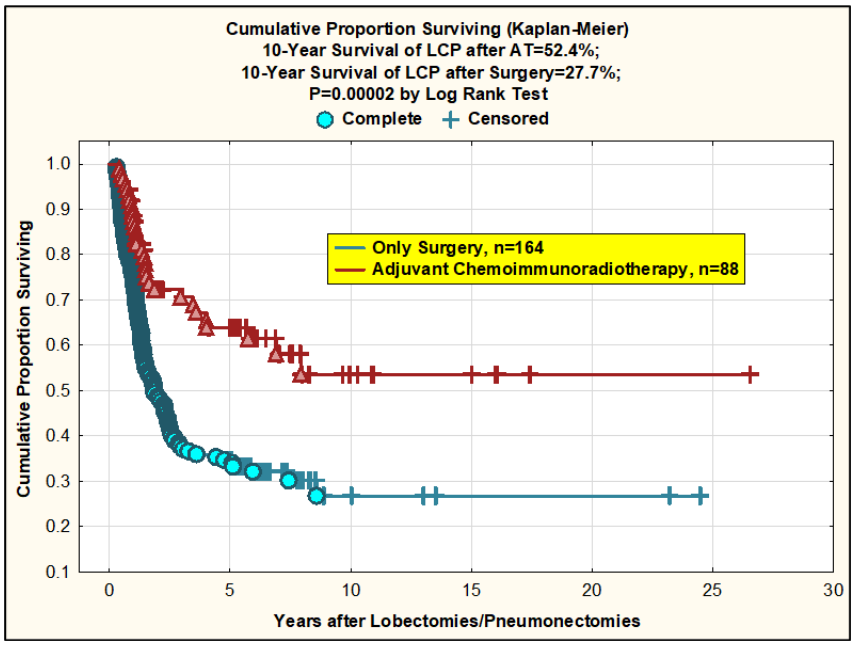

Figure 4 10-year survival of LCP with N1-2 after adjuvant chemoimmunoradiotherapy in group A 52.4%, n=88 was significantly better than in group B (only surgery) 27.7%, n=164 (P=0.00002 by log-rank test)

Third, for the AT significantly improved 10YS (52.4% vs. 27.7%) (P=0.00002 by log-rank test) only for LCP with N1-2 (Fig.4).

Fourth, we revealed 73.4% 10YS for female LCP versus 63.4% for male LCP after surgery (P=0.0289 by log-rank test) (Fig.5).

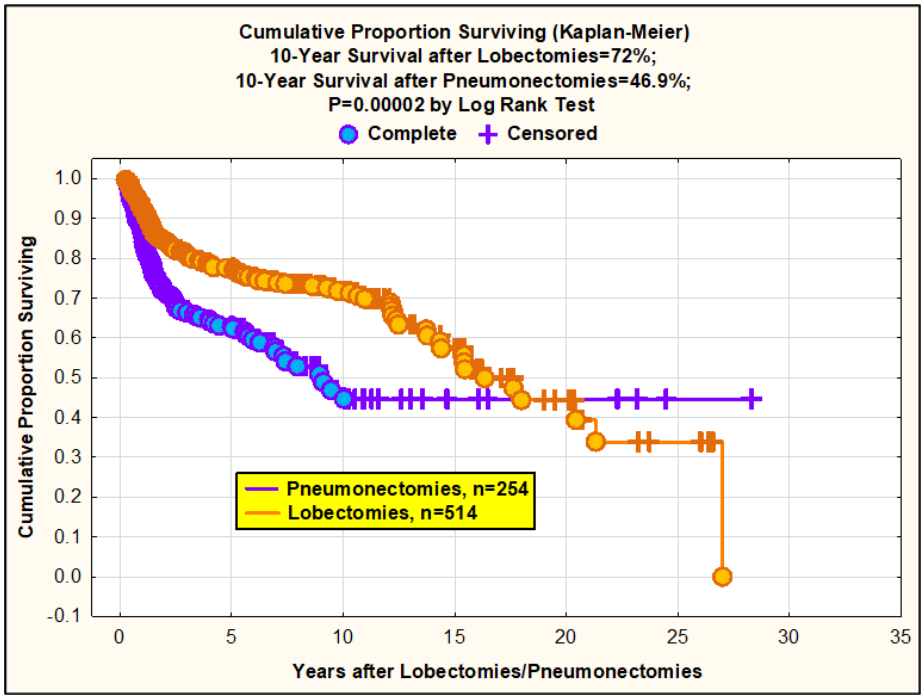

Figure 5 10-year survival of LCP after lobectomies 72% (n=514) was significantly better compared with LCP after pneumonectomies 46.9% (n=254) (P=0.00002 by log-rank test)

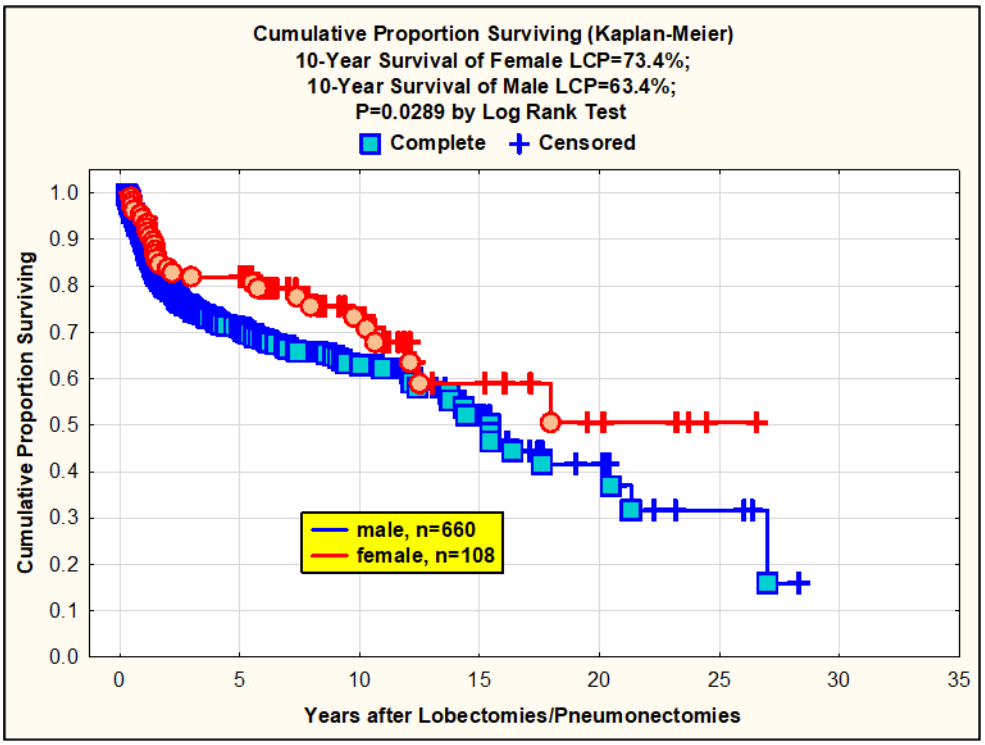

Figure 6 10-year survival of females LCP after surgery 73.4% (n=108) was significantly better compared with males LCP after surgery 63.4% (n=660) (P=0.0289 by log-rank test)

In the fifth we found 72% 10YS for LCP after lobectomies versus 46.9% for LCP after pneumonectomies (P=0.00002 by log-rank test) (Fig.6).

All parameters were analyzed in a multivariate Cox model. In accordance with this Cox model the sixteen variables significantly explained 10-year survival of LCP after surgery: phase transition (PT) early—invasive LC, PT N0---N12, LC characteristics (histology, G1-3), adjuvant chemoimmunoradiotherapy, blood cell subpopulations, hemostasis parameters, cell ratio factor (ratio between blood cell subpopulations and cancer cell population), etc. (Table 1).

Table 1 Results of multivariate proportional hazard Cox regression modeling in prediction of LCP survival after lobectomies and pneumonectomies (n=768)

Cox Proportional Hazards Results, LCP T1-4N0-2M0, n=768	Parameter Estimate	Standard Error	Chi-square	P value
Thrombocytes/Cancer Cells	-0.00550	0.001579	12.14276	0.000493
Healthy Cells/Cancer Cells	0.07391	0.024958	8.77037	0.003062
Adjuvant Chemoimmunoradiotherapy	-1.13036	0.201727	31.39806	0.000000
Phase Transition N0---N12	1.12121	0.144416	60.27584	0.000000
Phase Transition Early-Invasive Cancer	-1.47130	0.341717	18.53830	0.000017
Histology	0.35066	0.084684	17.14621	0.000035
G1-3	0.36443	0.087580	17.31503	0.000032
Color Index	-2.18363	0.917025	5.67018	0.017256
Glucose	-0.32526	0.078234	17.28559	0.000032
Prothrombin Index	0.03372	0.006854	24.20847	0.000001
Bilirubin	0.05124	0.018274	7.86319	0.005045
Recalcification Time	-0.00444	0.001711	6.73236	0.009468
Heparin Tolerance	0.00392	0.000662	35.06287	0.000000
Thrombocytes (tot)	0.00172	0.000341	25.43339	0.000000
Monocytes	-0.05039	0.024421	4.25828	0.039059
Weight	-0.03451	0.008725	15.64460	0.000076

For comparative purposes, clinicomorphological variables of LCP (n=344: 145 10-year survivors and 199 losses) were tested by neural networks computing (4-layer perceptron) (Fig. 7) (Table 2). To obtain a more exact analysis 424 patients being alive less than 10 years after radical procedures without relapse were excluded from the sample. Obviously, analyzed data provide significant information about LC prediction. High accuracy of classification (10-year survivors vs. losses) was achieved 100% (baseline error=0.000, area under ROC curve=1.0). In other words, it remains formally possible that at least 11 of these factors might predate neoplastic generalization: PT early—invasive LC (rank=1), thrombocytes/CC (2), PT N0—N12 (3), segmented neutrophils/CC (4), healthy cells/CC (5), lymphocytes/CC (6), erythrocytes/CC (7), stick neutrophils/CC (8), eosinophils/CC (9), leucocytes/CC (10), monocytes/CC (11). Moreover, bootstrap simulation confirmed the paramount value of Cell Ratio Factors, PT N0---N12 and PT early---Invasive GC (Table 3). 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 and imitating modeling of system "LC—patient homeostasis" in terms of synergetics (Fig. 9-12). This also proves the first results received earlier in the work [9,24] (Fig. 8). Presence of the two phase transitions is evidently shown on Kohonen self-organizing neural networks maps (Fig. 13).

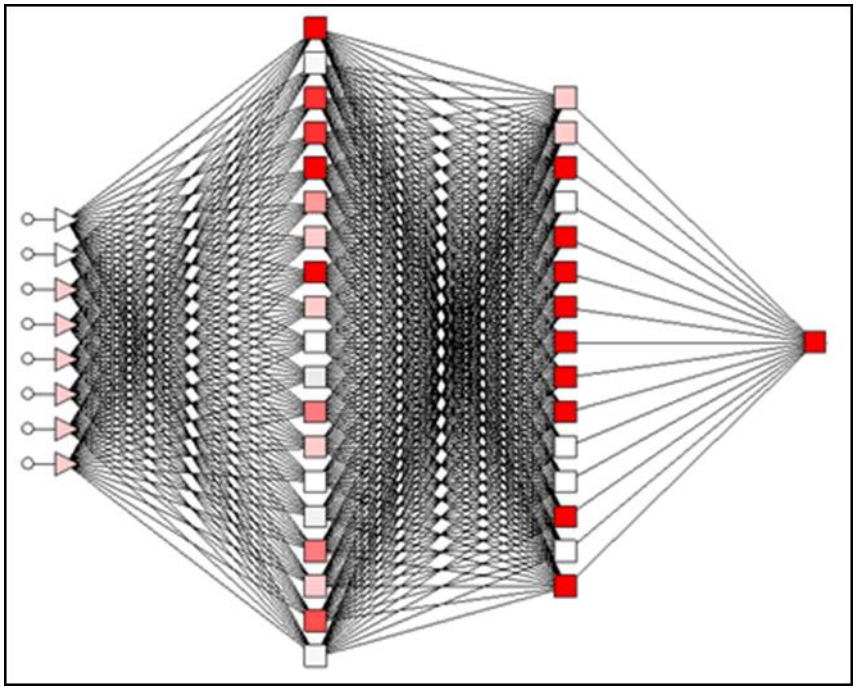

Figure 7 Configuration of neural networks: 4-layer perceptron

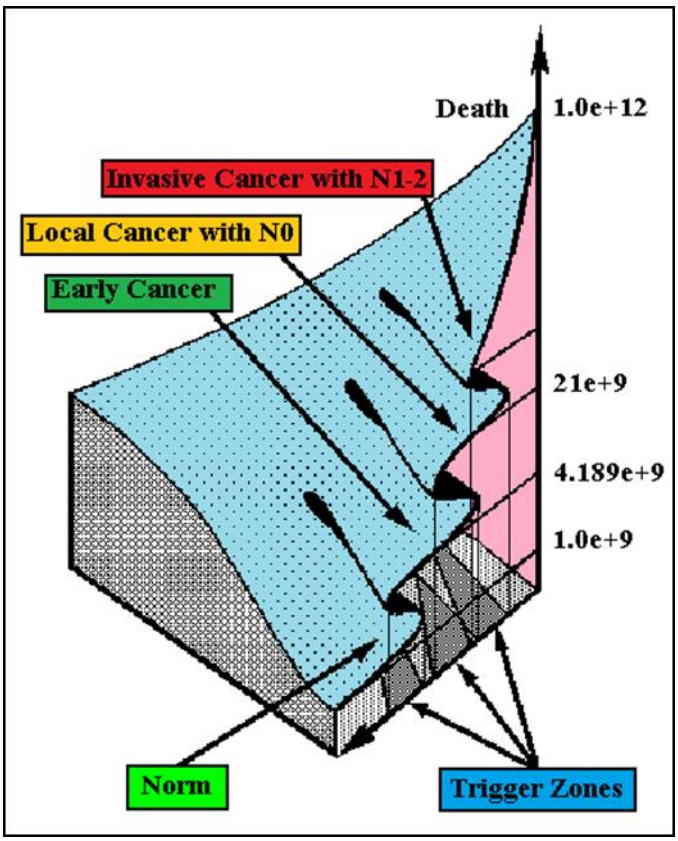

Figure 8 Lung Cancer Dynamics: Presence of the two phase transitions "early lung cancer—invasive lung cancer" and "lung cancer with N0—cancer with N1-2" in terms of synergetics

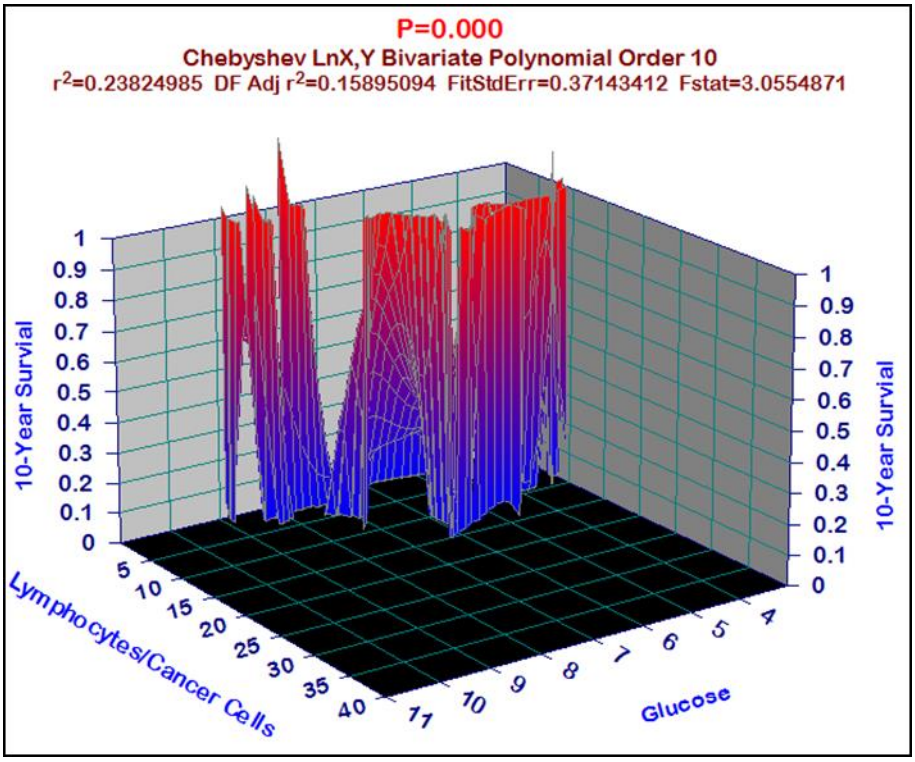

Figure 9 Prognostic equation model of 10-year survival of lung cancer patients (n=344), blood Lymphocytes/Cancer Cells and blood glucose (P=0.000)

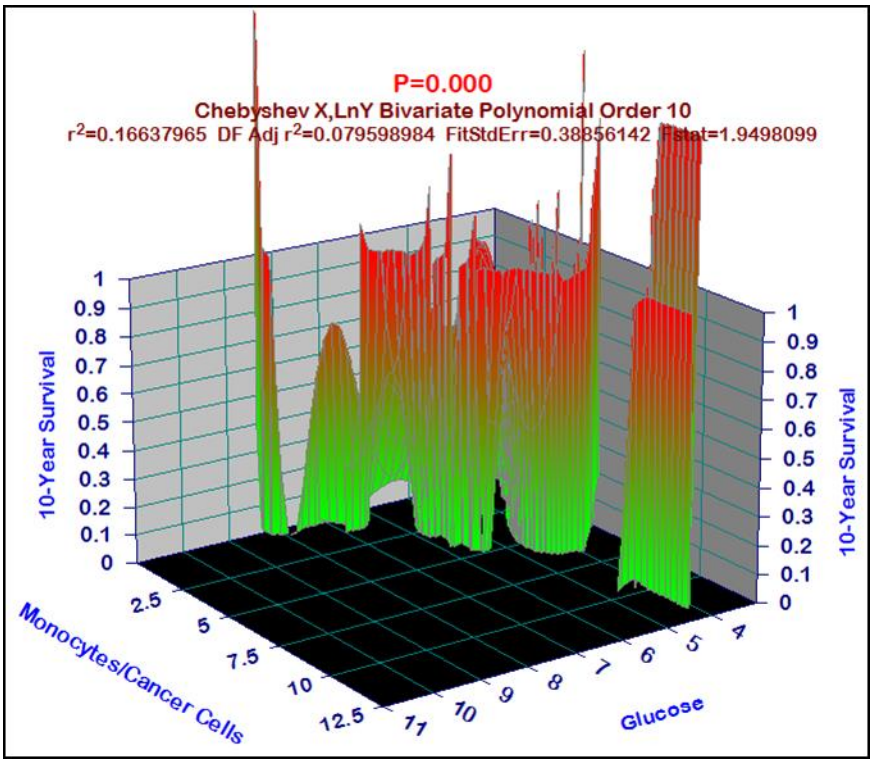

Figure 10 Prognostic equation model of 10-year survival of lung cancer patients (n=344), blood Monocytes/Cancer Cells and blood glucose (P=0.000)

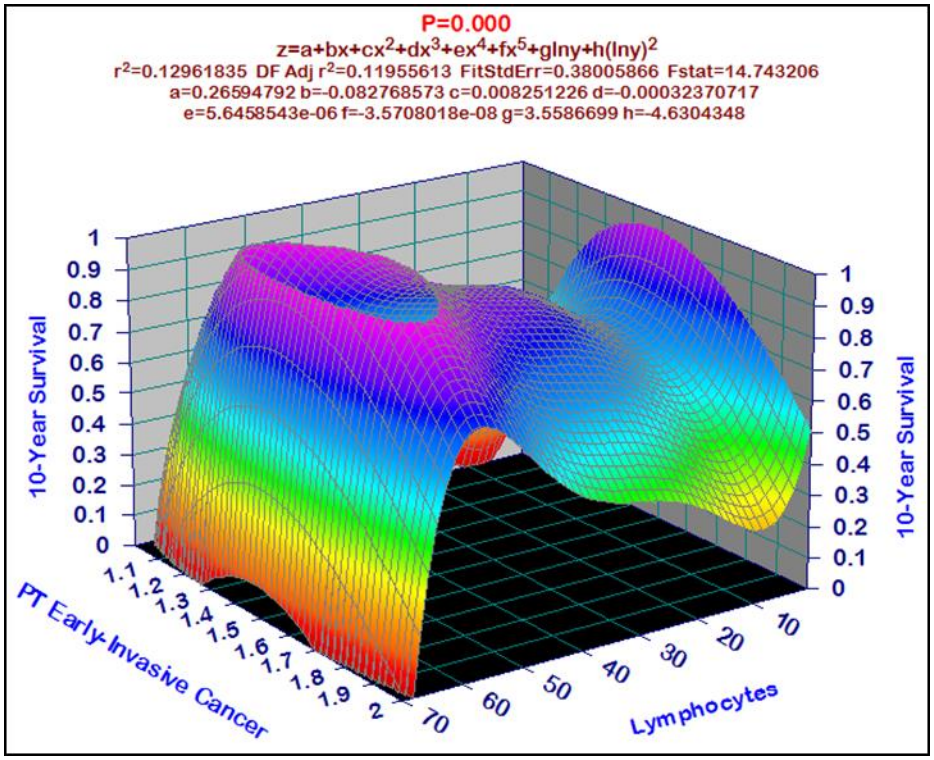

Figure 11 Prognostic equation model of 10-year survival of lung cancer patients (n=344), phase transition early—invasive lung cancer and blood lymphocytes (P=0.000)

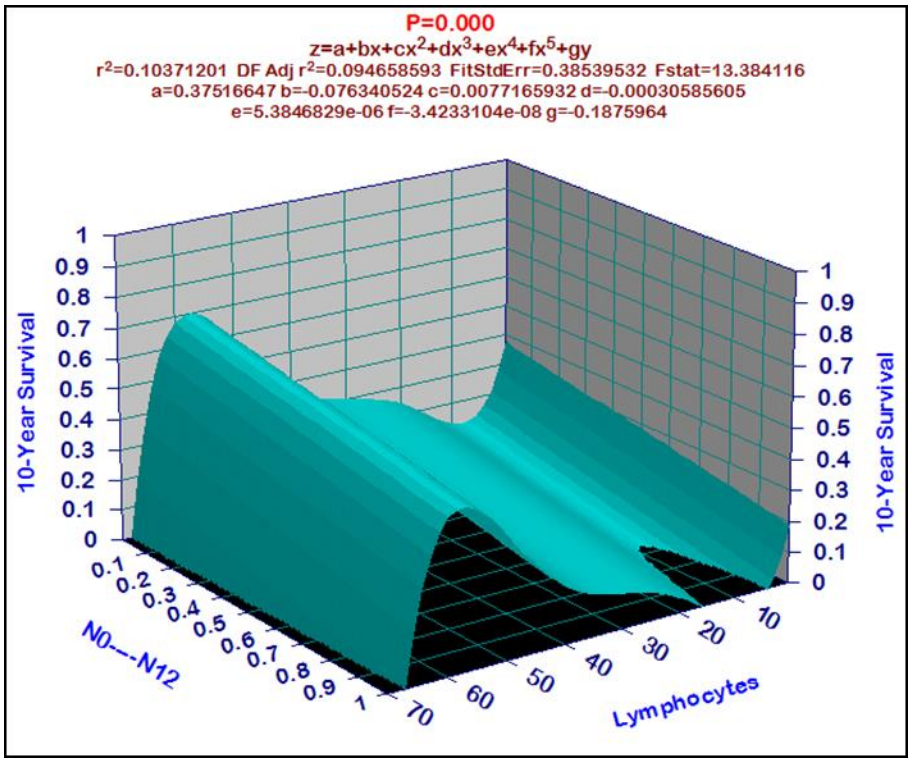

Figure 12 Prognostic equation model of 10-year survival of lung cancer patients (n=344), phase transition N0---N12 and blood lymphocytes (P=0.000)

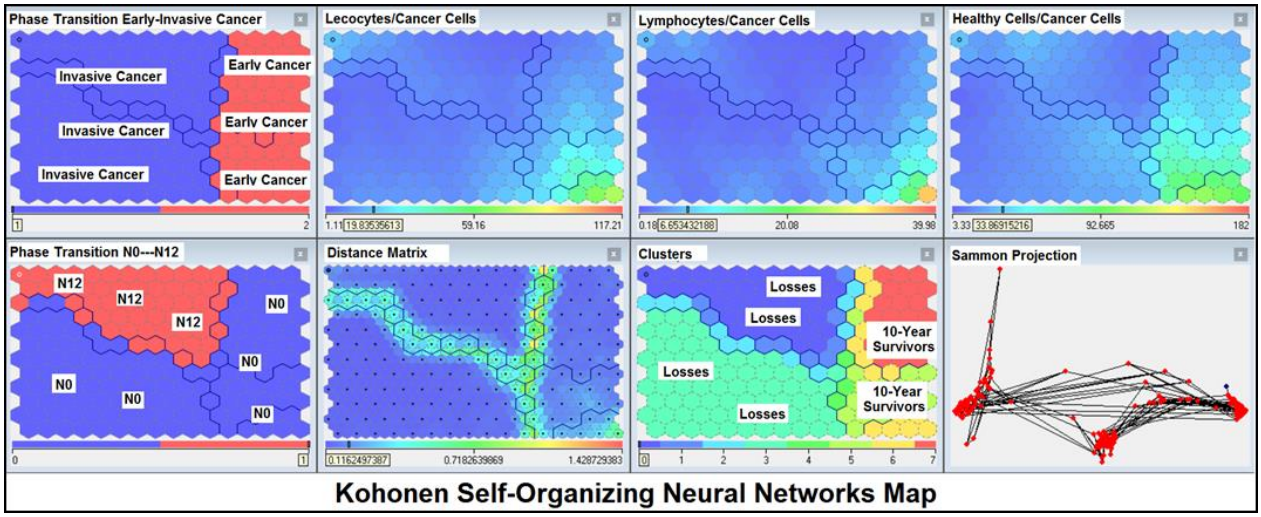

Figure 13 Results of Kohonen self-organizing neural networks computing in prediction of 10-year survival of LCP after surgery (n=344)

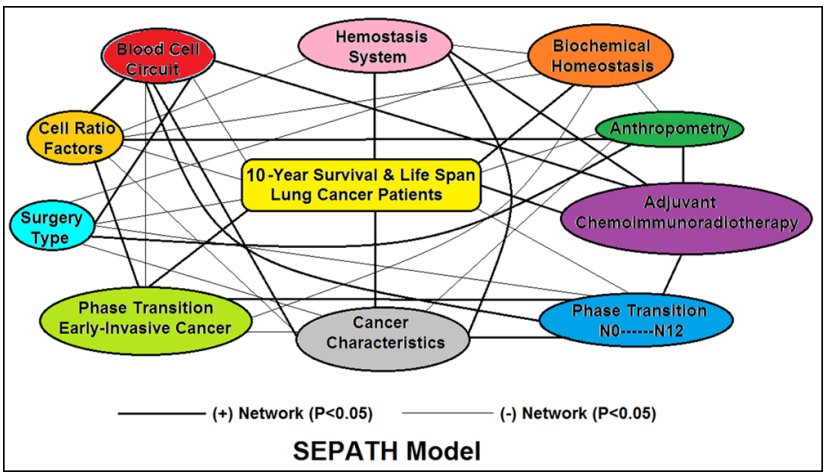

Figure 14 Significant networks between LCP (n=344) survival, cancer characteristics, blood cell circuit, cell ratio factors, hemostasis system, biochemic and anthropometric data, phase transition "early cancer—invasive cancer", phase transition "cancer with N0—cancer with N1-2" and treatment protocols (SEPATH model)

Table 2 Results of neural networks computing in prediction of 10-year survival of LCP after lobectomies and pneumonectomies (n=344: 145 10-year survivors and 199 losses)

Neural Networks: n=344; Baseline Error=0.000; Area under ROC Curve=1.000; Correct Classification Rate=100%	**Rank**	**Sensitivity**
Phase Transition Early--Invasive Cancer	1	11646
Thrombocytes/Cancer Cells	2	7184
Phase Transition N0--N12	3	6656
Segmented Neutrophils/Cancer Cells	4	4154
Healthy Cells/Cancer Cells	5	4407
Lymphocytes/Cancer Cells	6	3993

Erythrocytes/Cancer Cells	7	3370
Stick Neutrophils/Cancer Cells	8	2963
Eosinophils/Cancer Cells	9	2224
Leucocytes/Cancer Cells	10	1566
Monocytes/Cancer Cells	11	1206

All of these differences and discrepancies were further investigated by structural equation modeling (SEPATH) as well as Monte Carlo simulation. From data, summarized in Fig. 14 it was revealed that the ten clusters significantly predicted 10YS and life span of LCP with N0-2 status (n=344): 1) PT early--invasive LC; 2) PT N0—N12; 3) Cell Ratio Factors; 4) LC characteristics; 5) blood cell circuit; 6) biochemical homeostasis; 7) hemostasis system; 8) surgery type; 9) adjuvant chemoimmunoradiotherapy; 10) anthropometric data.

Table 3 Results of bootstrap simulation in prediction of 10-year survival of LCP after lobectomies and pneumonectomies (n=344: 145 10-year survivors and 199 losses)

Bootstrap Simulation n=344 Significant Factors (Number of Samples=3333)	**Rank**	**Kendall'Tau-A**	**P<**
Lymphocytes/Cancer Cells	1	0.269	0.000
Leucocytes/Cancer Cells	2	0.223	0.000
Healthy Cells/Cancer Cells	3	0.211	0.000
Erythrocytes/Cancer Cells	4	0.193	0.000
Thrombocytes/Cancer Cells	5	0.192	0.000
Lymphocytes (tot)	6	0.183	0.000
Segmented Neutrophils/Cancer Cells	7	0.173	0.000
Tumor Size	8	-0.118	0.000
Monocytes/Cancer Cells	9	0.111	0.000
PT Early---Invasive Cancer	10	0.107	0.000
Lymphocytes (%)	11	0.105	0.000
Segmented Neutrophils (%)	12	-0.102	0.000
Lymphocytes (abs)	13	0.096	0.000
Prothrombin Index	14	-0.094	0.001
T1-4	15	-0.094	0.001
PT N0---N12	16	-0.092	0.001
Procedures Type	17	0.087	0.01
Histology	18	0.076	0.01
Stick Neutrophils/Cancer Cells	19	0.073	0.01

Eosinophils/Cancer Cells	20	0.067	0.05
Age	21	-0.067	0.05
Fibrinogen	22	-0.052	0.05

4. 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 [4,5]. 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 gene therapy [2,6,12,21,22]. 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, statistical 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 [1,14-20,24].

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 and 10-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, radiotherapy and immunotherapy. 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 [1,4,23].

The most widely accepted treatment strategy for lymph node metastasis is the subsequent initiation of multimodality treatment, including surgery, adjuvant/neoadjuvant chemotherapy, chemoradiation or chemoimmunoradiotherapy[3-5,8]. 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 [24]. 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, immunomodulators and check-point inhibitors after surgery. The results of the present research will offer guidance for the design of future studies.

Optimal treatment strategies for LCP are: 1) screening and early detection of LC; 2) availability of experienced thoracic 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.

Conclusion

10-Year survival of LCP after radical procedures significantly depended on:1) phase transition early-invasive cancer; 2) phase transition N0--N12; 3) cell ratio factors; 4) blood cell circuit; 5) biochemical factors; 6) hemostasis system; 7) adjuvant chemoimmunoradiotherapy; 8) lung cancer characteristics; 9) anthropometric data;10) surgery type.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

All patients signed a written informed consent included in the study, approved by the local Institutional Review Board.

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