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Optimization of Management for Esophageal Cancer Patients with Stage T1-4N0-2M0

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Abstract
OBJECTIVE: Search of best management for esophageal cancer (EC) patients (ECP) (T1-4N0-2M0) was realized. METHODS: We analyzed data of 499 consecutive ECP (age=56.3±8.9 years; tumor size=6.3±3.4 cm) radically operated and monitored in 1975-2017 (m=365, f=134; esophagogastrectomies (EG) Garlock=280, EG Lewis=219, combined EG with resection of pancreas, liver, diaphragm, aorta, VCS, colon transversum, lung, trachea, pericardium, splenectomy=147; adenocarcinoma=284, squamous=205, mix=10; T1=92, T2=113, T3=171, T4=123; N0=234, N1=69, N2=196; G1=140, G2=123, G3=236; early EC=73, invasive=426; only surgery=382, adjuvant chemoimmunoradiotherapy-AT=117: 5-FU+thymalin/taktivin+radiotherapy 45-50Gy). Multivariate Cox modeling, clustering, SEPATH, Monte Carlo, bootstrap and neural networks computing were used to determine any significant dependence. RESULTS: Overall life span (LS) was 1763.2±2213.7 days and cumulative 5-year survival (5YS) reached 47.3%, 10 years – 40.7%, 20 years – 29.8%. 148 ECP lived more than 5 years (LS=4382.9±2551 days), 80 ECP – more than 10 years (LS=6027.2±2445.6 days). 223 ECP died because of EC (LS=630.2±320.5 days). AT significantly improved 5YS (67.7% vs. 43.1%) (P=0.00002 by log-rank test). Cox modeling displayed (Chi2=283.82, df=18, P=0.0000) that 5YS of ECP significantly depended on: phase transition (PT) N0—N12 in terms of synergetics, cell ratio factors (ratio between cancer cells and blood cells subpopulations), G, age, AT, localization, blood cells, prothrombin index, coagulation time, residual nitrogen (P=0.000-0.048). Neural networks, genetic algorithm selection and bootstrap simulation revealed relationships between 5YS and PT N0--N12 (rank=1), PT early-invasive EC (rank=2), T (3), AT (4), prothrombin index (5), glucose (6), healthy cells/CC (7), thrombocytes/CC (8), erythrocytes/CC (9), segmented neutrophils/CC (10), lymphocytes/CC (11), monocytes/CC (12). Correct prediction of 5YS was 100% by neural networks computing. CONCLUSIONS: Optimal management for ECP are: 1) screening and early detection of EC; 2) availability of experienced thoracoabdominal surgeons because of complexity of radical procedures; 3) aggressive en block surgery and adequate lymph node dissection for completeness; 4) precise prediction; 5) adjuvant chemoimmunoradiotherapy for ECP with unfavorable prognosis.

1. Introduction

The high mortality rate associated with esophageal cancer (EC) is primarily due to the high incidence of late stage and the lack of curative management for the majority of EC patients (ECP). Up to 70-90% of ECP present with stage III-IV disease. The role of adjuvant chemotherapy or chemoradiotherapy after complete esophagectomies in ECP with stage II-III remains controversial [1]. Moreover, the optimal treatment plan in

general and optimal approach for adjuvant chemoradiotherapy in particular has not been defined and long-term prognosis of ECP especially with stage III-IVA remains poor, because of local relapse and distant metastases, with the real 5-year survival rate after radical procedures only 20-35% [2]. One of the approaches developed aggressive en-block surgery and extensive lymphadenectomy for completeness. Another of the modern approaches developed to enhance the efficacy of surgery is the combination of chemotherapy, irradiation and immunotherapy or gene therapy which offers the advantage of exposing EC cell population for drugs and immune factors thus obviating cancer cell-cycle cytotoxic and host-immunoprotective effects [3]. 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.

2. Patients and Methods

We conducted this study from September 1975 to March 2017. 499 consecutive ECP (male – 365, female – 134; age=56.3±8.9 years, tumor size=6.3±3.4 cm) (mean±standard deviation) entered this trial. Patients were not considered eligible if they had stage IV (nonregional lymph nodes metastases and distant metastases), previous treatment with chemotherapy, immunotherapy or radiotherapy or if there were two primary tumors of the time of diagnosis. Patients after non-radical procedures, postoperative died ECP 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, roentgenoesophagogastroscopy, computed tomography scan of thorax, abdominal ultrasound, fibroesophagogastroscopy, electrocardiogram. Computed tomography scan of abdomen, liver and bone radionuclide scan were performed whenever needed. All ECP were diagnosed with histologically confirmed EC. All had measurable tumor and ECOG performance status 0 or 1. Before any treatment each patient was carefully examined by medical panel composed of surgeon, chemotherapeutist and radiologist 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 radical procedures. We performed two types procedures: 219 complete esophagogastrectomies with lesser and partially major omentum with preservation of right gastroepiploic vessels and lymph node dissection through separate abdominal and right thoracic incision (Ivor-Lewis) and 280 - through left thoracoabdominal incision (Garlock). The present analysis was restricted to ECP with complete resected tumors with negative surgical resection margin and with N1 and celiac lymph node metastases (N2). Surgical complete resection consisted of esophagogastrectomy with one-sage esophagogastroplasty with intrapleural anastomosis in 364, and with anastomosis on the neck in 135. EC was localized in lower third of esophagus in 317, middle third - in 56, upper third – in 73, total – in 53. Among these, 147 ECP underwent combined and extensive radical procedures with the resection of diaphragm, pericardium, lung, liver left lobe, splenectomy, pancreas, aorta, vena cava superior, colon transversum. 317 patients underwent lymph nodal D2-dissection (in terms of gastric cancer surgery). Extensive lymph nodal D3-dissection was performed in 182 ECP. Routine two-field lymphadenectomy (in terms of EC surgery) was performed in 317, three-field – in 182. All ECP were postoperatively staged according to the TNMG-classification. Histological examination showed adenocarcinoma in 284, squamos cell carcinoma - in 205 and mixed carcinoma - in 10 patients. The pathological T stage was T1 in 92, T2 - in 113, T3 - in 171, T4 - in 123 cases; the pathological N stage was N0 in 234, N1 - in 69, N2 - in 196 patients. The tumor differentiation was graded as G1 in 140, G2 - in 123, G3 - in 236 cases. After surgery postoperative chemoimmunoradiotherapy were accomplished ECP in ECOG performance status 0 or 1.

All patients (499 ECP) were divided between the two protocol treatment: 1) surgery and adjuvant chemoimmunoradiotherapy (117 ECP – group A) (age=56.0±7.4 years; males - 81, females - 36; tumor size=7.4±3.7 cm); 2) surgery alone without any adjuvant treatment (382 ECP – group B) (age=56.4±9.4 years; males - 284, females - 98; tumor size=6.0±3.2 cm) – the control group.

117 ECP were performed adjuvant chemoimmunoradiotherapy consisted of chemoimmunotherapy (5-6 cycles) and thoracic radiotherapy (group A). 1 cycle of bolus chemotherapy was initiated 3-5 weeks after complete esophagectomies and consisted of fluorouracil 500 mg/m^2 intravenously for 5 days. Immunotherapy consisted thymalin or taktivin 20 mg intramuscularly on days 1, 2, 3, 4 and 5. These immunomodulators 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 [4]. The importance must be stressed of using immunotherapy in combination with chemotherapy and radiotherapy, because immune dysfunctions of the cell-mediated and humoral response were induced by tumor, surgical trauma, chemotherapy and radiation [3]. Such immune deficiency induced generalization of EC and compromised the long-term therapeutic result. In this sense immunotherapy shielded human organism from side and adverse effects of basic treatment. Concurrent radiotherapy (^{60}CO; ROKUS, Russia) with a total tumor dose 45-50 Gy starting 5-7 weeks after surgery. 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 jugularis to 8 cm below the carina. The lower mediastinum and upper abdomen were included in cases of primary tumors in the lower third of esophagus or N2. 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.

During chemoimmunoradiotherapy 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, chest roentgenography. Endoscopy and abdominal ultrasound were done every 6-month for the first 3 years and yearly after that. 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, tumor size. Survival curves were estimated by the Kaplan-Meier method. Differences in curves between groups of ECP were evaluated using a log-rank test. Multivariate proportional hazard Cox regression, structural equation modeling (SEPATH), Monte Carlo, bootstrap simulation and neural networks computing were used to determine any significant dependence [3, 5, 6, 7, 8, 9, 10]. 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), STATISTICA and STATISTICA Neural Networks program (Stat Soft, Inc., Tulsa, OK, the USA), MATHCAD (MathSoft, Inc., Needham, MA, the USA), SIMSTAT (Provalis Research, Inc., the USA). All tests were considered significant when the resulting P value was less than 0.05.

3. Results

For the entire sample of 499 patients overall life span (LS) was 1763.2±2213.7 days (95% CI, 1568.5-1958.0; median=793). General cumulative 5 year survival was 47.3%, 10-year survival – 40.7%, 20-year survival – 29.8%. 245 ECP (49.1%) were alive, 148 ECP lived more than 5 years (LS=4382.9±2551 days) and 80 ECP – more than 10 years (LS=6027.2±2445.6 days) without any features of EC progressing. 223 ECP died because of EC during the first 5 years after surgery (LS=630.2±320.5 days).

For the 117 ECP in adjuvant chemoimmunoradiotherapy arm (group A), overall LS was 1859.3±2475.1 days (95% CI, 1406.1-2312.5; median=687). For the 382 ECP in the control (group B), overall LS was 1733.8±2129.9 days (95% CI, 1519.6-1948.1; median=811). The overall cumulative 5-year survival of ECP for group A was 67.7% and was significantly superior compared to 43.1% for group B (P=0.00002 by log-rank test) (Figure 1).

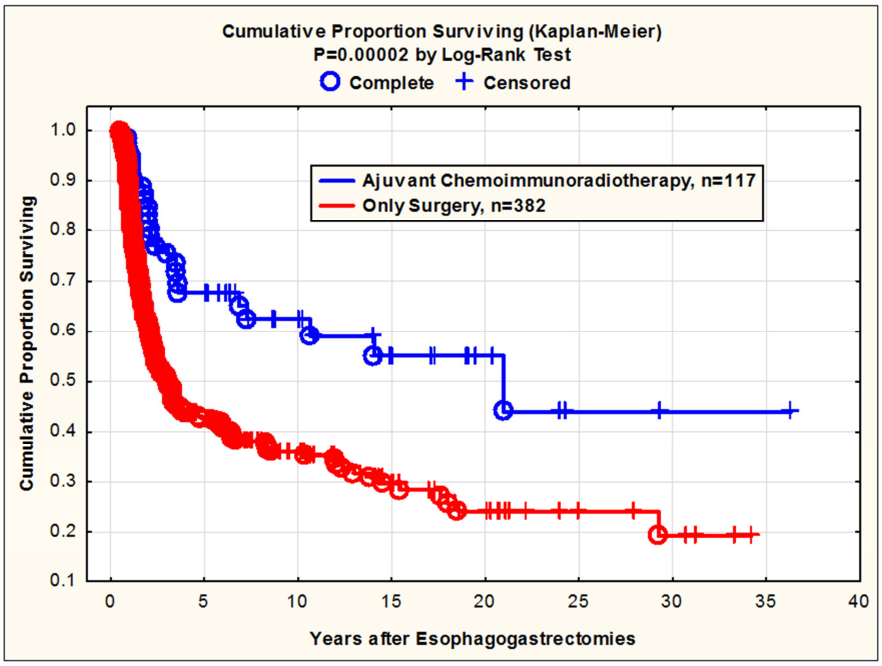

Figure 1. *Survival of ECP after esophagogastrectomies in group A (adjuvant chemoimmunoradiotherapy) (n=117) and B (surgery alone) (n=382). Survival of ECP in group A was significantly better compared with group B (P=0.023 by log-rank).*

Accordingly, the overall 10-year survival for group A was 62.3% and was much better compared to 35.9% for group B.

It is necessary to pay attention on the two very important prognostic phenomenons. First, 100% 5-years survival for ECP with the early cancer as against 38% for the others ECP after esophagogastrectomies (P=0.00000 by log-rank test) (Figure 2).

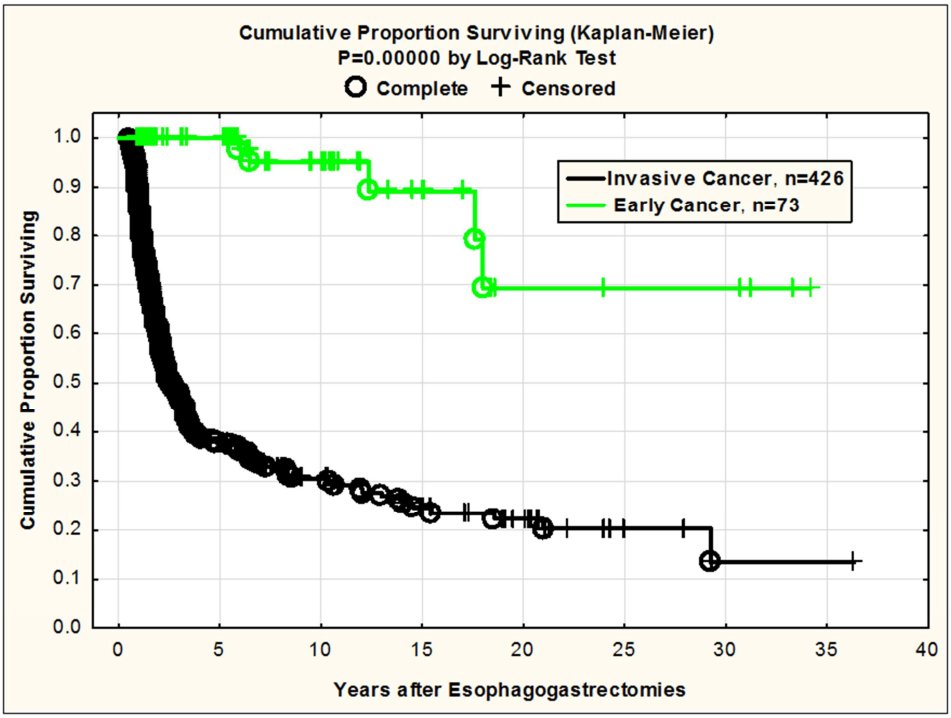

Figure 2. *Survival of ECP with early cancer (n=73) was significantly better compared with invasive cancer (n=426) (P=0.00000 by log-rank).*

We understand as the early cancer the tumor up to 2 cm in diameter, witch invades submucosa without lymph node and distant metastases [10]. Correspondingly, the overall 10-year survival for ECP with the early cancer was 95.1% and was significantly better compared to 308% for others ECP.

Second, good 5-year survival for ECP with N0 (68.4%) as compared with ECP with N1-2 (5-year survival was 27.7%) after radical procedures (P=0.00000 by log-rank test) (Figure 3).

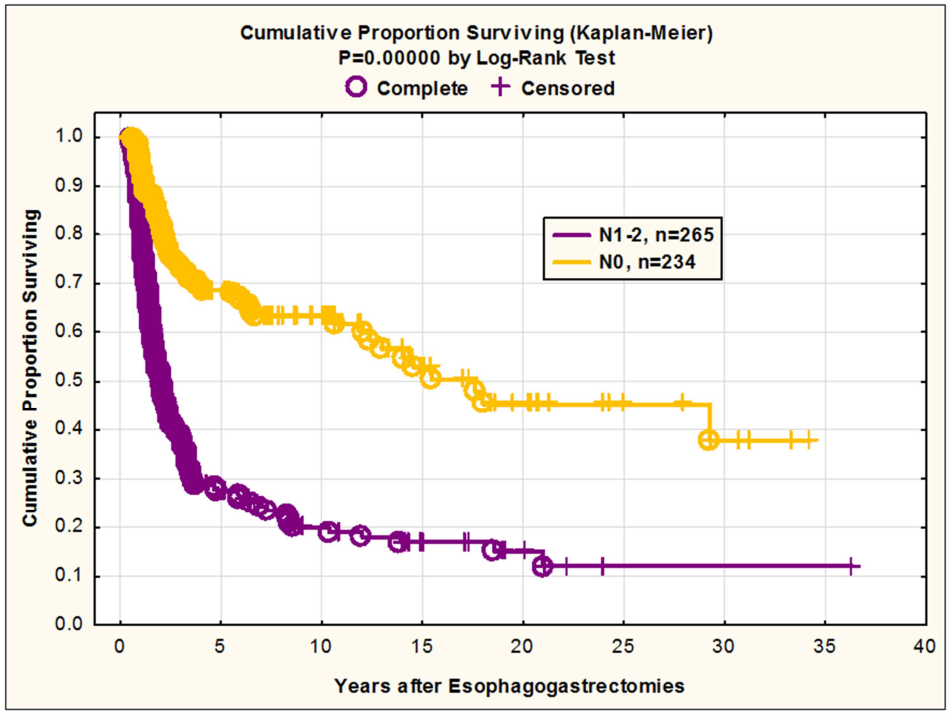

Figure 3. *Survival of ECP with N0 (n=234) was significantly better compared with N1-2 metastases (n=265) (P=0.00000 by log-rank).*

Table 1. *Results of multivariate proportional hazard Cox regression modeling in prediction of ECP survival after esophagogastrectomies (Chi2=283.823; df=18; P=0.0000; n=499).*

Factors	Standard - Error	t-value	p	Risk ratio
Segmented Neutrophils (%)	0.019874	3.54882	0.000388	1.07308
Coagulation Time	0.000408	3.98026	0.000069	1.00163
Residual Nitrogen	0.012015	4.54340	0.000006	1.05611
Prothrombin Index	0.006795	3.38158	0.000722	1.02325
Segmented Neutrophils (abs)	0.108797	-2.80952	0.004965	0.73663
Lymphocytes (abs)	0.279282	3.13763	0.001705	2.40195
Phase Transition N0---N1-2	0.157731	3.83253	0.000127	1.83036
Age	0.007710	2.46343	0.013767	1.01917
G1-3	0.083201	2.97580	0.002924	1.28093
Adjuvant Chemoimmunoradiotherapy	0.207624	-4.94425	0.000001	0.35824
Phase Transition Early---Invasive Cancer	0.563160	0.66659	0.505038	1.45557
Eosinophils (tot)	0.149638	3.27512	0.001057	1.63245
Leucocytes/Cancer Cells	1.099462	-2.61308	0.008977	0.05653
Stick Neutrophils/Cancer Cells	1.135675	3.18936	0.001427	37.41531
Segmented Neutrophils/Cancer Cells	1.113770	2.42686	0.015235	14.92394
Lymphocytes/Cancer Cells	1.136820	2.20179	0.027687	12.21954
Monocytes/Cancer Cells	1.219576	3.63945	0.000274	84.65498
Localization: Upper/3 vs. Others/3	0.194984	-1.98089	0.047612	0.67961

Accordingly, the overall 10-year survival for ECP with N0 was 63% and was significantly superior compared to 20.3% for ECP with lymph node metastases.

All parameters were analyzed in a Cox model. In accordance with this Cox model (global χ^2=283.82; Df=18; P=0.00000), the eighteen variables significantly explained 5-year survival of ECP after complete esophagogastrectomies: phase transition "early---invasive cancer", phase transition N0---N1-2, adjuvant chemoimmunoradiotherapy, age, G1-3, cell ratio factors (ratio between cancer cells and blood cells subpopulations), tumor localization (upper/3 vs. others/3), blood cell circuit (segmented neutrophils, lymphocytes, eosinophils), prothrombin index, coagulation time, residual nitrogen (P=0.000-0.048) (Table 1).

Table 2. *Results of neural networks computing in prediction of 5-year survival of ECP after esophagogastrectomies (n=371: 5-year survivors=148 and losses=223) (Baseline Error=0.000; Area under ROC Curve=1.000; Correct Classification Rate=100%).*

Factors	Rank	Sensitivity
Phase Transition N0---N12	1	4301
Phase Transition Early---Invasive Cancer	2	3489
T1-4	3	3181
Adjuvant Chemoimmunoradiotherapy	4	2922
Prothrombin Index	5	2258
Glucose	6	1636
Healthy Cells/Cancer Cells	7	1530
Thrombocytes/Cancer Cells	8	1273
Erythrocytes/Cancer Cells	9	1008
Segmented Neutrophils/Cancer Cells	10	442
Lymphocytes/Cancer Cells	11	427
Monocytes/Cancer Cells	12	351

Table 3. *Results of bootstrap simulation in prediction of 5-year survival of ECP after esophagogastrectomies (n=371: 5-year survivors=148 and losses=223).*

Significant Factors (Number of Samples=3333)	Rank	Kendal Tau-A	P
Tumor Size	1	-0.272	0.000
Healthy Cells/Cancer Cells	2	0.270	0.000
T1-4	3	-0.269	0.000
Erythrocytes/Cancer Cells	4	0.261	0.000
Leucocytes/Cancer Cells	5	0.248	0.000
Thrombocytes/Cancer Cells	6	0.247	0.000
Lymphocytes/Cancer Cells	7	0.241	0.000
Segmented Neutrophils/Cancer Cells	8	0.229	0.000
Residual Nitrogen	9	-0.222	0.000
Phase Transition N0---N12	10	-0.213	0.000
Monocytes/Cancer Cells	11	0.207	0.000
Coagulation Time	12	-0.201	0.000
Phase Transition Early---Invasive Cancer	13	-0.179	0.000
Stick Neutrophils/Cancer Cells	14	0.159	0.000
Chlorides	15	0.157	0.000
Eosinophils/Cancer Cells	16	0.144	0.000
Tumor Growth	17	-0.121	0.001
G1-3	18	-0.118	0.001
Erythrocytes	19	0.086	0.05
Glucose	20	0.085	0.05
Prothrombin Index	21	-0.081	0.05
Localization	22	0.079	0.05
Weight	23	0.076	0.05

For comparative purposes, clinicomorphological variables of ECP (n=371: 148 5-year survivors and 223 losses) were

tested by neural networks computing. For more exact analysis 128 patients were excluded from the sample, which were alive less than 5 years after complete esophagectomies without relapse. Multilayer perceptron was trained by BFGS method. Obviously, analyzed data provide significant information about EC prediction. High accuracy of classification – 100% (5-year survivors vs. losses) was achieved in analyzed sample (baseline error=0.000, are under ROC curve=1.0). In other words it remains formally possible that reviled twelve factors might predate neoplastic generalization: N-status, T-status, prothrombin index, blood glucose, adjuvant treatment and cell ratio factors (Table 2). Bbootstrap simulation confirmed significant dependence between 5-year survival of ECP after radical procedures and all recognized variables (Tables 3). Moreover, bootstrap simulation confirmed the paramount value of cell ratio factors.

It is necessary to note very important law. Transition of the early cancer into the invasive cancer as well as the cancer with N0 into the cancer with N1-2 has the phase character. These results testify by mathematical (Holling-Tenner) and imitating modeling of system "EC—patient homeostasis" in terms of synergetics (Figure 4).

This also proves the first results received earlier in the works [3, 10]. Presence of two phase transitions is evidently shown on Kohonen self-organizing neural networks maps (Figure 5).

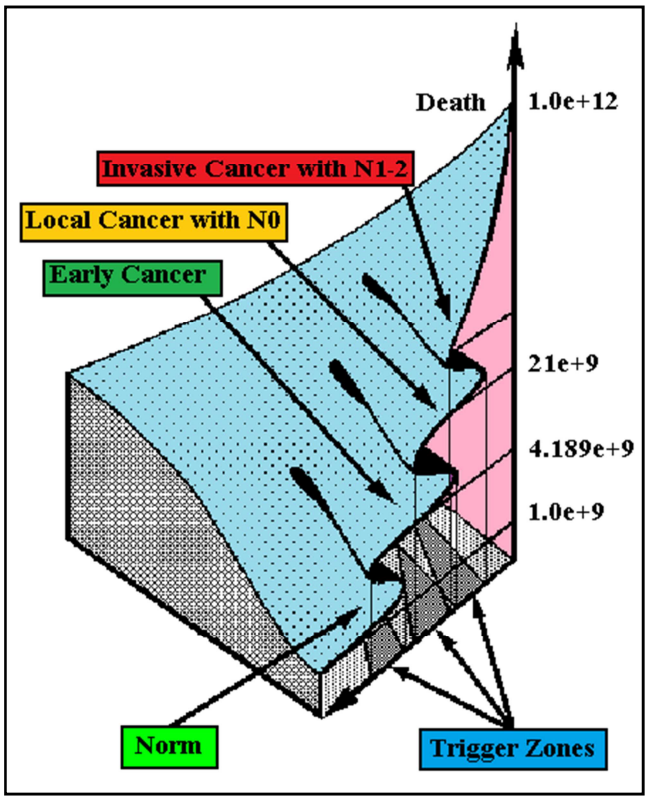

Figure 4. *Presence of the two phase transitions "early cancer—invasive cancer" and "cancer with N0—N1-2" in terms of synergetics.*

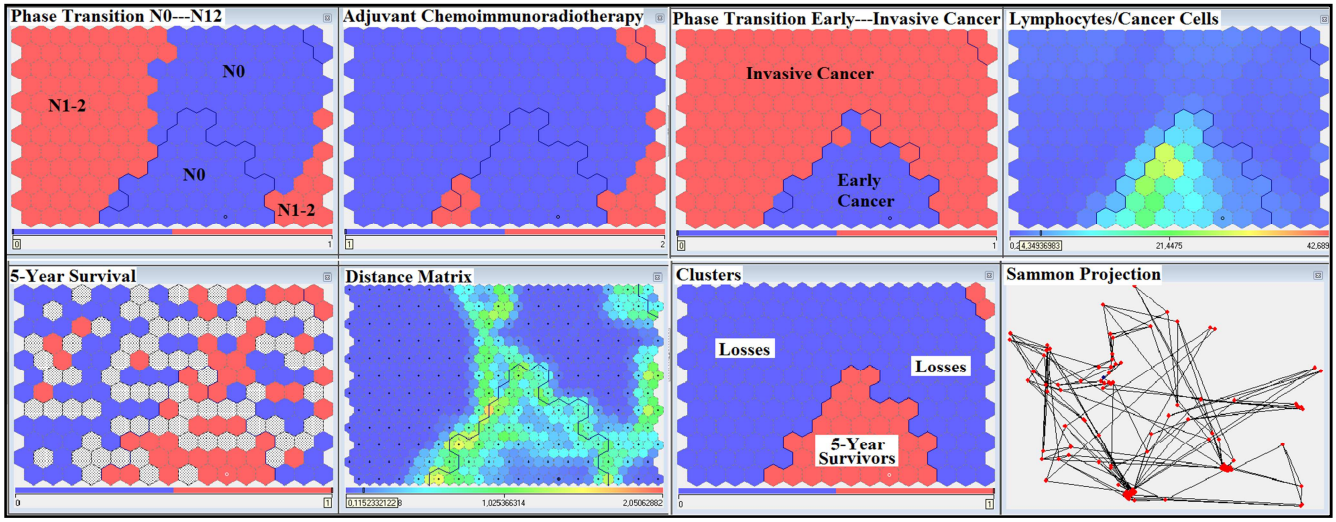

Figure 5. *Results of Kohonen self-organizing neural networks computing in prediction of ECP Survival after Esophagectomies (n=371).*

All of these differences and discrepancies were further investigated by structural equation modeling (SEPATH) as well as Monte Carlo simulation. From data, summarized in Figure 6, it was revealed that the ten clusters significantly predicted 5-year survival and life span of ECP after esophagectomies: 1) phase transition "early EC—invasive EC"; 2) phase transition N0---N1-2; 3) EC characteristics; 4) cell ratio factors; 5) blood cell circuit; 6) biochemical homeostasis; 7) hemostasis system; 8) adjuvant chemoimmunoradiotherapy; 9) tumor localization in the esophagus; 10) anthropometric data (Figure 6).

It is necessary to pay attention, that both phase transitions strictly depend on blood cell circuit and cell ratio factors.

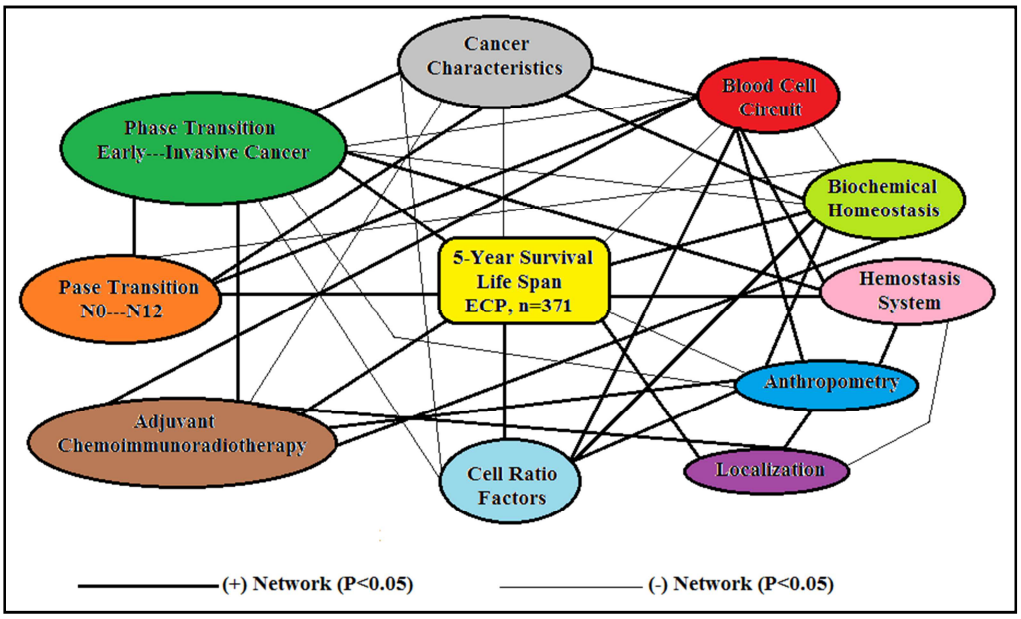

Figure 6. *Significant networks between ECP (n=371) survival, cancer characteristics, blood cell circuit, cell ratio factors, hemostasis system, biochemic and anthropometric data, cancer localization, phase transition "early cancer—invasive cancer", phase transition "cancer with N0—N1-2" and treatment protocols (SEPATH network model).*

4. Discussion

Treatment of ECP is extremely difficult problem. On the one hand, the esophagus cancer surgery demands masterly surgical technique and always will remain the privilege of very experienced professionals [11]. Actually surgical removal of tumor and its metastases remains basic management of this very aggressive cancer giving the real chance for recovery in spite of quite intensive researches developed during the last 30 years in terms of chemotherapy, radiotherapy, immunotherapy and gene therapy [1, 2, 12]. On the other hand, the effectiveness of complete esophagectomy already reached its limit and leaves much to be desired: the average real 5-year survival rate of radically operated ECP even after combined and extensive procedures is 30-40% and practically is not improved during the past 30-40 years, as the great majority of patients has already EC with advance stage [3, 10, 13]. 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 EC is rather inexact and approximate with the big errors.

Central goal of the present research was to estimate the efficiency of complete esophagectomies with lymphadenectomies and adjuvant chemoimmunoradiotherapy after radical surgery. The importance must be stressed of using complex system analysis, artificial intelligence (neural networks computing) 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. While huge merit of simulation modeling is the identification of dynamics of any supersystem on the hole in time [3, 10].

Although there is no consensus on adjuvant treatment after radical procedures the two of the most commonly employed strategies are surgery alone and adjuvant (neoadjuvant) chemoradiotherapy with or without immunotherapy. In the last 10-15 years a number of new drugs have been shown to have good activity against EC, including mitomycin C, cisplatin, doxetacel, etc. [14, 15, 16]. On the other hand new immunomodulators, new adoptive immunotherapeutic modalities with lymphokine-activated killer cells, tumor-infiltrating lymphocytes and high-dose interleukins have been developed and antitumor effect have been successfully demonstrated in advanced malignancies [17, 18].

Theoretically chemoimmunotherapy is 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 micrometastases [3, 10]. This is typical clinical situation for ECP with N1-2 after complete esophagogastrectomies. Present research only confirmed this axiom.

In summary, when adjuvant chemoimmunoradiotherapy is applied to complete esophagogastrectomies for EC 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 ECP with advance stage are thought to be potentially good candidates for adjuvant chemoimmunoradiotherapy as the majority of these patients would be expected to have EC progressing.

As regards the early EC that it is all quite clear. For these patients only radical surgery is absolutely sufficient and

adjuvant treatment is no need. From this it follows the paramount importance of screening and early detection of EC.

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

5. Conclusion

Optimal treatment strategies for ECP are: 1) screening and early detection of EC; 2) availability of very experienced surgeons because of complexity radical procedures; 3) aggressive en block surgery and adequate lymph node dissection for completeness; 4) precise prediction and 5) adjuvant chemoimmunoradiotherapy for ECP with unfavorable prognosis.

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