Esophageal Cancer: Optimization of Management

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Abstract: *Objective*: We examined factors associated with generalization of esophageal cancer (EC) after complete esophagectomies (E).

Methods: We analyzed data of 126 consecutive EC patients (ECP) (age = 56.8±7.9 years) operated and monitored in 1975-2007 (males = 98, females = 28; E Ivor-Lewis = 89, E Garlock = 37; adenocarcinoma = 93, squamos = 31, mix = 2; T1 = 25, T2 = 38, T3 = 29, T4 = 34; N0 = 55, N1 = 23, M1a = 48; only surgery-S = 97, adjuvant chemoimmunoradiotherapy-AT = 29: 5-FU+ thymalin/taktivin+radiotherapy 45-50Gy). Cox regression, clustering, structural equation modeling, Monte Carlo, bootstrap, neural networks computing were used to determine any significant dependence.

Results: General cumulative 5-year survival (5YS) was 50.5%, 10-year survival - 38.3%. 39 ECP (31%) lived more than 5 years, 17 ECP - 10 years. 55 ECP (43.7%) died because of EC. AT significantly improved ECP 5YS (P = 0.023). Cox modeling displayed that 5YS significantly depended on: T, N, histology, stage, combined procedures, AT, age, blood cell subpopulations (P = 0.000-0.039). Neural networks, genetic algorithm and bootstrap simulation revealed relationships between 5YS of ECP and N (rank = 1), sex, EC growth, T, histology, combined procedures, G, blood residual nitrogen, hemorrhage time, blood chlorides, AT, neutrophils, tumor size, thrombocytes, monocytes. Correct prediction of 5YS was 100% by neural networks computing.

Conclusions: Optimal treatment strategies are: screening/early detection; availability of experienced surgeons; aggressive surgery; precise prediction; AT for ECP with unfavorable prognosis.

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 IIB-IV disease. The role of adjuvant chemotherapy or chemoradiotherapy after complete esophagectomies in ECP with stage II-IVA 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 involves aggressive en-block surgery and complete lymphadenectomy. 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.

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PATIENTS AND METHODS

We performed a retrospective review of prospectively collected database of patients undergoing an esophagectomy for EC between September 1975 and March 2007. 126 consecutive ECP (male – 98, female – 28; age = 56.8±7.9 years, tumor size = 5.4±2.5 cm) (mean±standard deviation) entered this trial. Patients were not considered eligible if they had stage IVB (nonregional lymph nodes metastases and distant metastases), previous treatment with chemotherapy, immunotherapy or radiotherapy or if there were two primary tumors at 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 a 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 surgery. We performed two types of procedures: 89 complete esophagectomies with lesser and partially major omentum with preserva-

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tion of right gastroepiploic vessels and lymph node dissection through separate abdominal and right thoracic incision (Ivor-Lewis) and 37 - 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 (M1A). Complete surgical resection consisted of esophagectomy with one-stage intrapleural esophagogastrostomy in 61, and with anastomosis on the neck in 65. EC was localized in lower third of esophagus in 61, middle third - in 48, upper third – in 17. Among these, 40 ECP underwent combined and extensive radical procedures with the resection of diaphragm, pericardium, lung, liver left lobe, splenectomy. The extent of lymphadenectomy in the upper abdominal compartment and lower posterior mediastinum was identical for all surgical approaches and comprised a suprapancreatic lymphadenectomy, including all lymph nodes along the common hepatic artery, celiac axis, and splenic artery toward the splenic hilum. The left gastric artery was always transected at its origin and remained with the specimen. Also included were all lymph nodes along the proximal two thirds of the lesser gastric curvature and the gastric fundus, left and right paracardiac nodes, distal paraesophageal nodes, and nodes in the lower posterior mediastinum up to the tracheal bifurcation. Patients with the right thoracoabdominal approach had an additional formal extended mediastinal lymphadenectomy comprising all nodes at the tracheal bifurcation along the left and right main stem bronchi, the upper mediastinal compartment, and along the left recurrent nerve. A systematic cervical lymphadenectomy was performed routinely for ECP with neck anastomosis. 59 patients underwent lymph nodal D2-dissection (in terms of gastric cancer surgery). Extensive lymph nodal D3-dissection was performed in 67 ECP. Routine two-field lymphadenectomy (in terms of EC surgery) was performed in 61, three-field – in 65. All ECP were postoperatively staged according to the TNMG-classification. Histological examination showed adenocarcinoma in 93, squamous cell carcinoma - in 31 and mixed carcinoma - in 2 patients. The pathological TNM stage was I in 22, IIA – in 24, IIB – in 13, III - in19, IVA – in 48 patients; the pathological T stage was T1 in 25, T2 - in 38, T3 - in 29, T4 - in 34 cases; the pathological N stage was N0 in 55, N1 - in 23, M1A - in 48 patients. The tumor differentiation was graded as G1 in 46, G2 - in 39, G3 - in 41 cases. After surgery postoperative chemoimmunoradiotherapy was accomplished in ECP with ECOG performance status 0 or 1.

All patients (126 ECP) were divided randomly between the two protocol treatment: 1) surgery and adjuvant chemoimmunoradiotherapy (29 ECP – group A) (age=57±1.6.5 years; males - 22, females - 7; tumor size=6.3±3.0 cm); 2) surgery alone without any adjuvant treatment (97 ECP – group B) (age=56.8±8.3 years; males - 76, females - 21; tumor size=5.1±2.3 cm) – the control group

Twenty-nine ECP received adjuvant chemoimmunoradiotherapy which 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/m2 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 longterm therapeutic result. In this sense, immunotherapy may have shielded the patient from adverse side effects of treatment. Concurrent radiotherapy (60CO; ROKUS, Russia) with a total tumor dose 45-50 Gy was started 5-7 weeks after surgery. Radiation consisted of single daily fractions of 180-200 cGy 5 days per week for 5 weeks. 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 M1A. 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, and 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, 5-10]. 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, USA), MATHCAD (MathSoft, Inc., Needham, MA, USA). All tests were considered significant when the resulting P value was less than 0.05.

RESULTS

For the entire sample of 126 patients overall life span (LS) was 1587.6±1650.3 days (mean ±standard deviation) (95% CI, 1296.6-1878.5; median = 895). General cumulative 5 year survival was 50.5%, 10-year survival – 38.3%. 64 ECP (50.8%) were alive till now, 39 ECP (31%) lived more than 5 years (LS = 3544.3±1712.5 days) and 17 ECP - 10 years (LS = 5000.1±1639 days) without any features of EC progressing. 55 ECP (43.7%) died because of EC during the first 5 years after surgery (LS = 621.4±366 days).

For the 29 ECP in adjuvant chemoimmunoradiotherapy arm (group A), overall LS was 1843.2±2083.4 days (95% CI, 1050.7±2635.7; median = 888). For the 97 ECP in the control (group B), overall LS was 1511.2±1501.5 days (95% CI, 1208.5-1813.8; median = 896) (P = 0.023 by log-rank test). The overall cumulative 5-year survival of ECP for group A reached 64.1% and was significantly superior compared to 47.0% for group B (P = 0.023 by log-rank test) (Fig. **1**).

It is necessary to pay attention to two very important prognostic phenomenons. First, we found 100 % 5-years survival for ECP with early cancer (T1N0) versus 40.5% for the others ECP after esophagectomies (P = 0.00001 by log-rank test) (Fig. **2**). Early esophageal cancer was defined, based on the final histopathologic report of the resection specimen, as tumor limited to the mucosa or submucosa and not extending into the muscular wall of the esophagus, up to 2 cm in diameter with N0 [10]. Patients with stage T1N0 did not receive adjuvant chemoimmunoradiotherapy. Correspondingly, the overall 10-year survival for ECP with the early cancer was 81% and was significantly better compared to 28% for others patients.

Second, we observed good 5-year survival for ECP with N0 (70%) as compared with ECP with N1-M1A (5-year survival was 33.1%) after radical procedures (P = 0.00002 by log-rank test) (Fig. **3**). Accordingly, the overall 10-year survival for ECP with N0 reached 60% and was significantly superior compared to 19% for ECP with lymph node metastases.

All parameters were analyzed in a Cox model. In accordance with this Cox model (global χ^2 = 124.1; Df = 31; P = 0.00000), the sixteen variables significantly explained 5-year survival of ECP after complete esophagectomies: stage, status of regional lymph nodes, tumor growth, adjuvant chemoimmunoradiotherapy, combined procedures, age, T1-4, histology and blood cell factors (percent of segmented neutrophils and lymphocytes, populations of leucocytes, eosinophils, stick and segmented neutrophils, lymphocytes and monocytes) (Table **1**).

For comparative purposes, clinicomorphological variables of ECP (n = 94: 39 5-year survivors and 55 losses) were tested by neural networks computing (4-layer perceptron) (Fig. **4**). For more exact analysis 32 patients were excluded from the sample, who were alive less than 5 years after complete esophagectomies without relapse. Multilayer perceptron was trained by Levenberg-Marquardt method (Fig. **5**). 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 = 0.001, are under ROC curve = 1.0). In other words it remains formally possible that reviled fifteen factors might predate neoplastic generalization: N-status, gender, EC growth, T-status, histology, type of combined procedures, G-status, blood residual nitrogen, hemorrhage time, blood chlorides, adjuvant chemoimmunoradio-

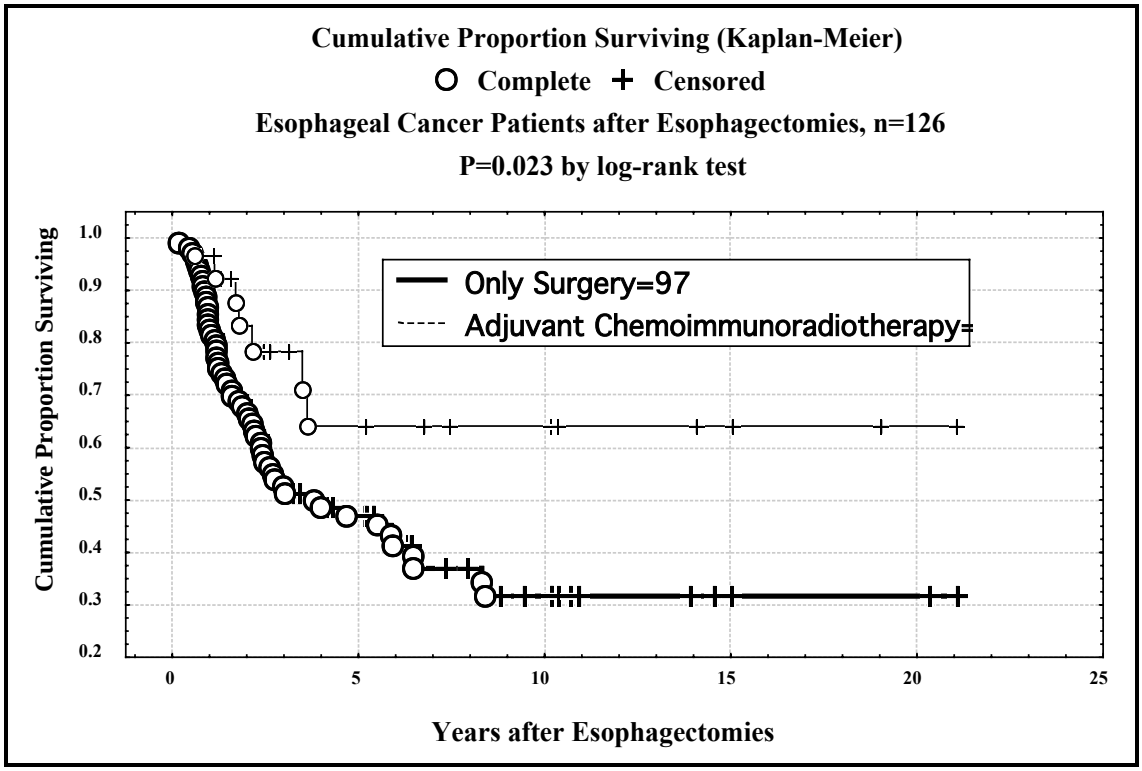

Fig. (1). Survival of ECP after esophagectomies in group A (adjuvant chemoimmunoradiotherapy) (n = 29) and B (surgery alone) (n = 97). Survival of ECP in group A was significantly better compared with group B (P = 0.023 by log-rank).

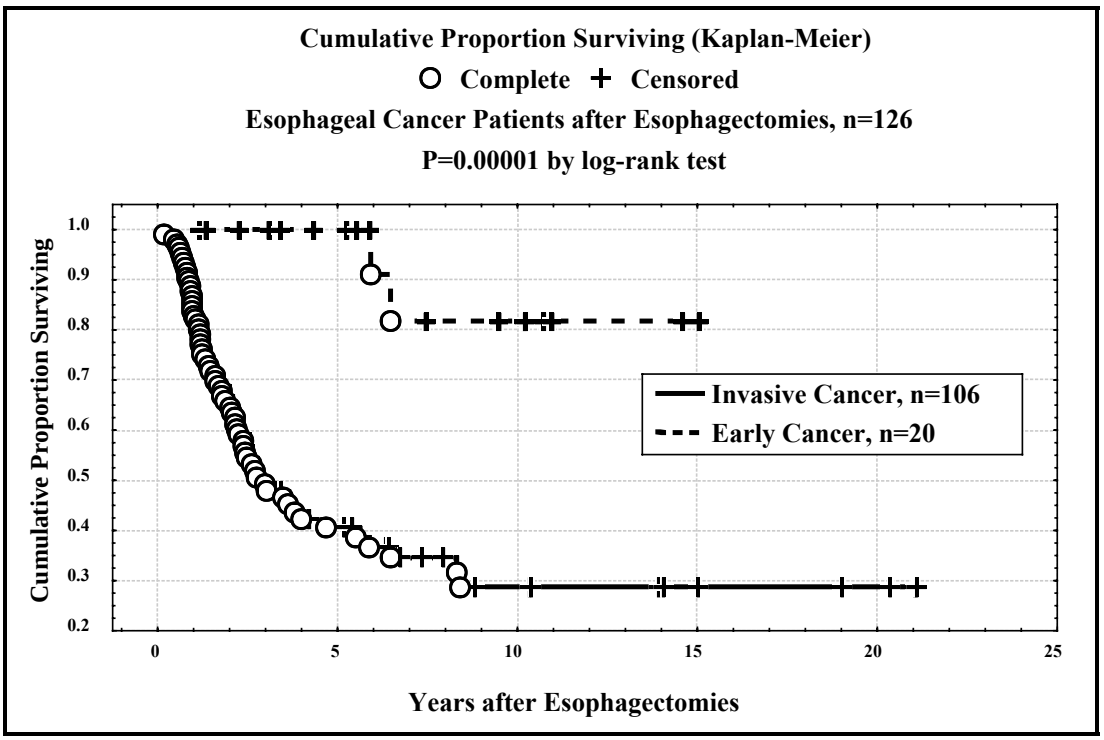

Fig. (2). Survival of ECP with early cancer (n = 20) was significantly better compared with invasive cancer (n = 106) (P = 0.00001 by log-rank).

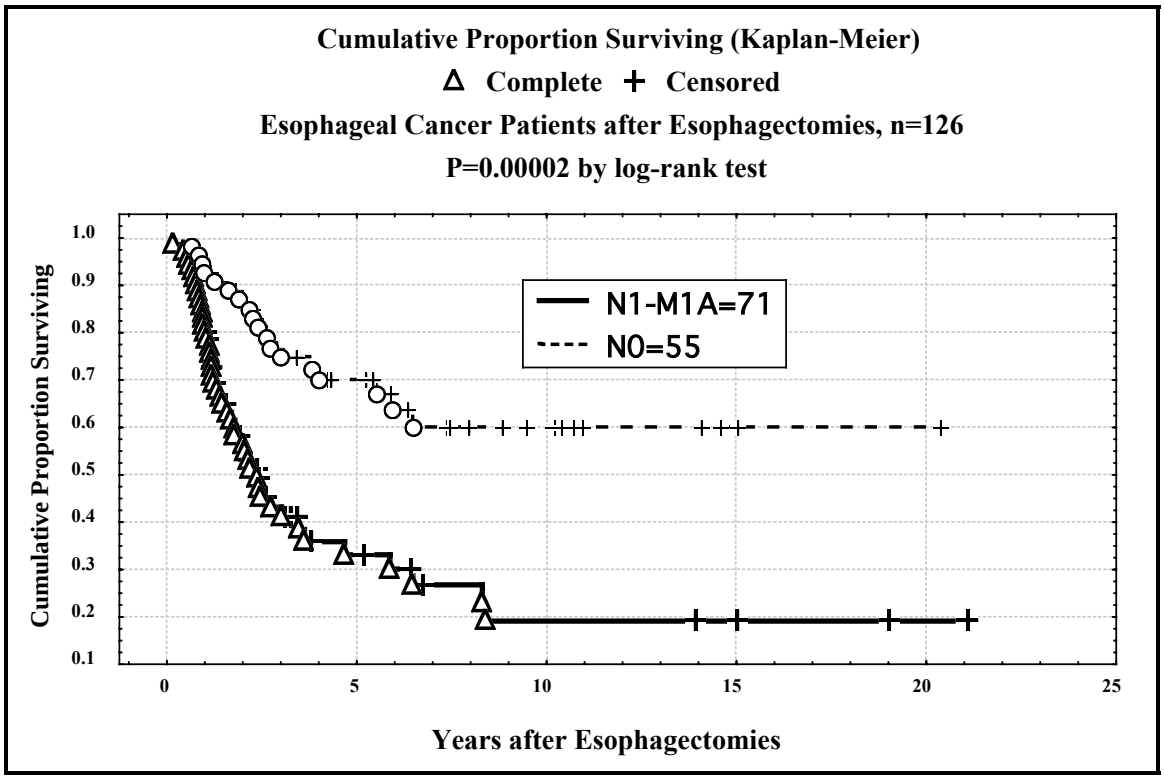

Fig. (3). Survival of ECP with N0 (n = 55) was significantly better compared with N1-M1A metastases (n = 71) (P = 0.00002 by log-rank).

therapy, percent of stick neutrophils in blood, tumor size, number of thrombocytes and monocytes in blood (Table **2**). Genetic algorithm selection and bootstrap simulation confirmed significant dependence between 5-year survival of ECP after radical procedures and all recognized variables (Tables **3** and **4**). Moreover, bootstrap simulation confirmed the paramount value of cell ratio factors (ratio between blood cell subpopulations and EC cell population).

Table 1. Results of Multivariate Proportional Hazard Cox Regression Modeling in Prediction of ECP Survival After Esophagectomies (n = 126)

Variables in the Equation	B	SE	Wald	df	P
Segmented Neutrophils (%)	0.225	0.089	6.335	1	0.012
Lymphocytes (%)	0.235	0.087	7.257	1	0.007
Histology			10.701	2	0.005
Histology(1)	-0.893	0.273	10.693	1	0.001
Histology(2)	-0.697	1.292	0.291	1	0.590
Tumor Growth			5.771	2	0.056
Tumor Growth(1)	2.672	1.114	5.754	1	0.016
Tumor Growth(2)	2.699	1.142	5.584	1	0.018
Adjuvant Chemoimmunoradiotherapy	-0.691	0.334	4.267	1	0.039
Combined Operation			15.710	5	0.008
Combined Operation(1)	-0.099	0.369	0.072	1	0.788
Combined Operation(2)	0.176	0.638	0.076	1	0.783
Combined Operation(3)	4.833	1.348	12.850	1	0.000
Combined Operation(4)	-0.209	0.699	0.090	1	0.765
Combined Operation(5)	-0.128	0.588	0.047	1	0.828
Leucocytes (tot)	-2.961	0.815	13.212	1	0.000
Eosinophils (tot)	3.220	0.747	18.553	1	0.000
Stick Neutrophils (tot)	3.320	0.789	17.698	1	0.000
Segmented Neutrophils (tot)	3.021	0.829	13.267	1	0.000
Lymphocytes (tot)	2.814	0.810	12.085	1	0.001
Monocytes (tot)	3.458	0.806	18.403	1	0.000
Leucocytes/Cancer Cells	0.104	0.111	0.871	1	0.351
Segmented Neutrophils/Cancer Cells	-0.263	0.148	3.144	1	0.076
T			16.809	3	0.001
T(1)	-1.796	0.857	4.392	1	0.036
T(2)	-2.799	0.721	15.054	1	0.000
T(3)	-0.782	0.467	2.809	1	0.094
N			19.295	3	0.000
N(1)	0.108	1.265	0.007	1	0.932
N(2)	2.470	1.324	3.479	1	0.062
N(3)	2.065	1.135	3.312	1	0.069
Stage			18.254	3	0.000
Stage(1)	0.914	0.912	1.004	1	0.316
Stage(2)	2.643	0.655	16.292	1	0.000
Stage(3)	0.882	0.720	1.501	1	0.220
Age	0.033	0.016	4.329	1	0.037
Erythrocytes/Cancer Cells	0.059	0.062	0.927	1	0.336

Table 2. Results of Neural Networks Computing in Prediction of 5-Year Survival of ECP After Esophagectomies (n = 94: 39 5-Year Survivors and 55 Losses)

NN	Esophageal Cancer Patients After Esophagectomies Factors	Rank	Sample Error	n = 94 Ratio
1	N	1	0.443	436.032
2	Gender	2	0.369	363.171
3	Esophagus Cancer Growth	3	0.294	288.790
4	T	4	0.267	262.995
5	Histology	5	0.252	248.158
6	Combined Procedures	6	0.209	205.320
7	G	7	0.173	170.081
8	Blood Residual Nitrogen	8	0.146	143.457
9	Hemorrhage Time	9	0.145	142.492
10	Blood Chlorides	10	0.122	119.974
11	Adjuvant Chemoimmunoradiotherapy	11	0.104	102.016
12	Stick Neutrophils (%)	12	0.082	80.696
13	Tumor Size	13	0.031	30.558
14	Thrombocytes (abs)	14	0.007	6.965
15	Monocytes (abs)	15	0.004	3.765
	Baseline Error		**0.001**	
	Area under ROC Curve		**1.000**	
	Correct Classification Rate (%)		**100.0**	

Table 3. Results of Neural Networks Genetic Algorithm Selection in Prediction 5-Year Survival of ECP After Esophagectomies (n = 94: 39 5-Year Survivors and 55 Losses)

NN	Esophageal Cancer Patients, n = 94 Factors	Useful for 5-Year Survival
1	Stick Neutrophils (%)	Yes
2	Monocytes (%)	Yes
3	Thrombocytes (abs)	Yes
4	ESS	Yes
5	Hemorrhage Time	Yes
6	Blood Residual Nitrogen	Yes
7	Blood Protein	Yes
8	Blood Chlorides	Yes
9	Tumor Size	Yes
10	Stick Neutrophils (abs)	Yes
11	T	Yes
12	N	Yes
13	Gender	Yes
14	G	Yes
15	Histology	Yes
16	Esophagus Cancer Growth	Yes
17	Adjuvant Chemoimmunoradiotherapy	Yes
18	Combined Procedures	Yes
19	Stick Neutrophils (tot)	Yes
20	Leucocytes/Cancer Cells	Yes

Table 4. Results of Bootstrap Simulation in Prediction of 5-Year Survival of ECP After Esophagectomies (n = 94: 39 5-Year Survivors and 55 Losses)

NN	Esophageal Cancer Patients After Esophagectomies n = 94	Rank	Number of Samples = 3333	>P
	Significant Factors		Kendall'Tau-A	
1	Erythrocytes/Cancer Cells	1	0.286	0.00004
2	Stage	2	-0.281	0.00008
3	Tumor Size	3	-0.274	0.0001
4	Healthy Cells/Cancer Cells	4	0.268	0.0002
5	T	5	-0.268	0.0002
6	Lymphocytes/Cancer Cells	6	0.250	0.0003
7	Leucocytes/Cancer Cells	7	0.235	0.0007
8	Coagulation Time	8	-0.215	0.001
9	N	9	-0.206	0.003
10	Eosinophils/Cancer Cells	10	0.206	0.003
11	Monocytes/Cancer Cells	11	0.204	0.004
12	Blood Residual Nitrogen	12	-0.197	0.007
13	Segmented Neutrophils/Cancer Cells	13	0.191	0.01
14	Thrombocytes/Cancer Cells	14	0.174	0.02
15	Blood Chlorides	15	0.171	0.02
16	Stick Neutrophils/Cancer Cells	16	0.164	0.03
17	Stick Neutrophils (%)	17	0.133	0.05

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-M1A has the phase character. These results testify by mathematical (Holling-Tanner) 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 works [3,10]. Presence of two phase transitions is evidently shown on Kohonen self-organizing neural networks maps (Fig. **8**).

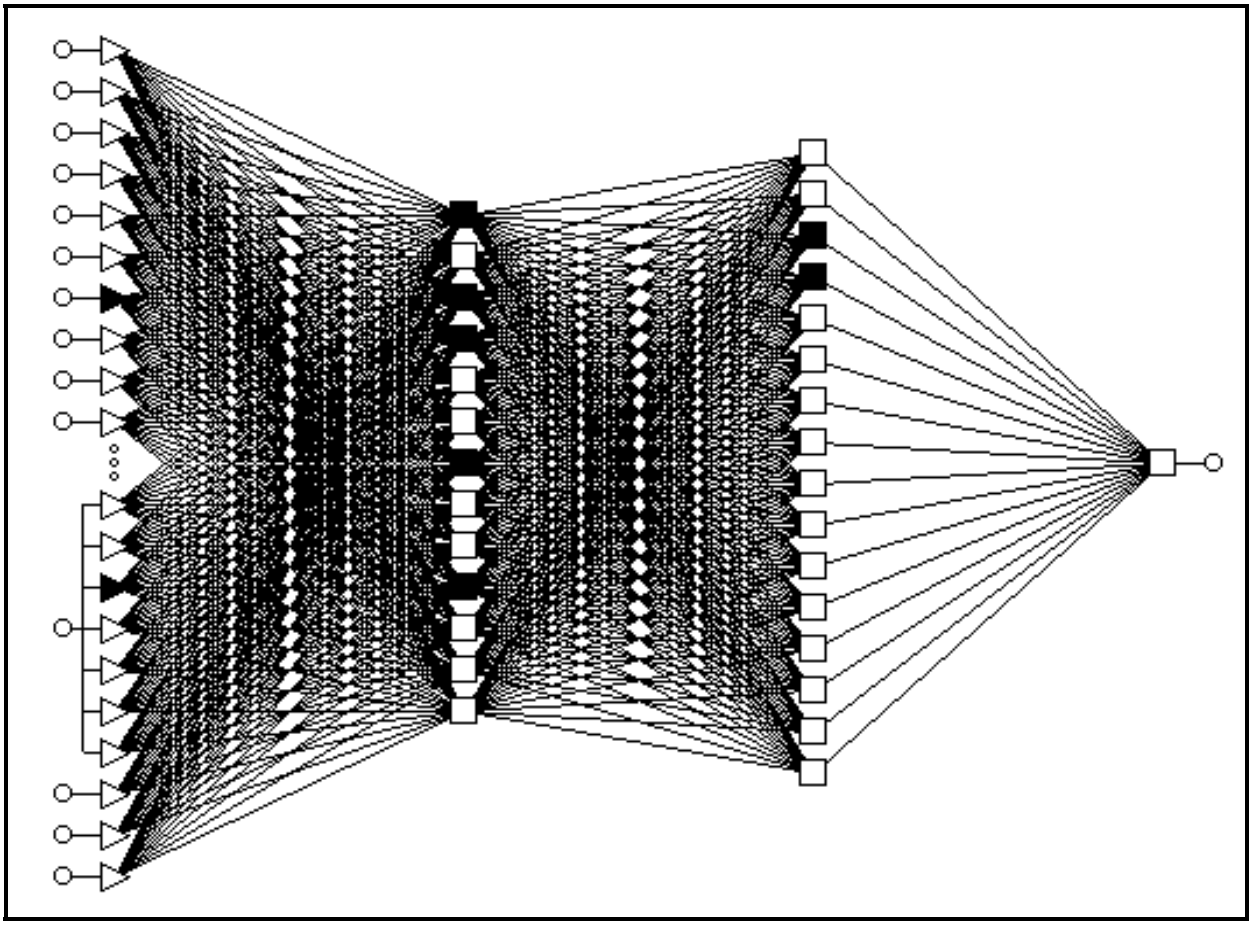

Fig. (4). Configuration of neural networks: 4-layer perceptron.

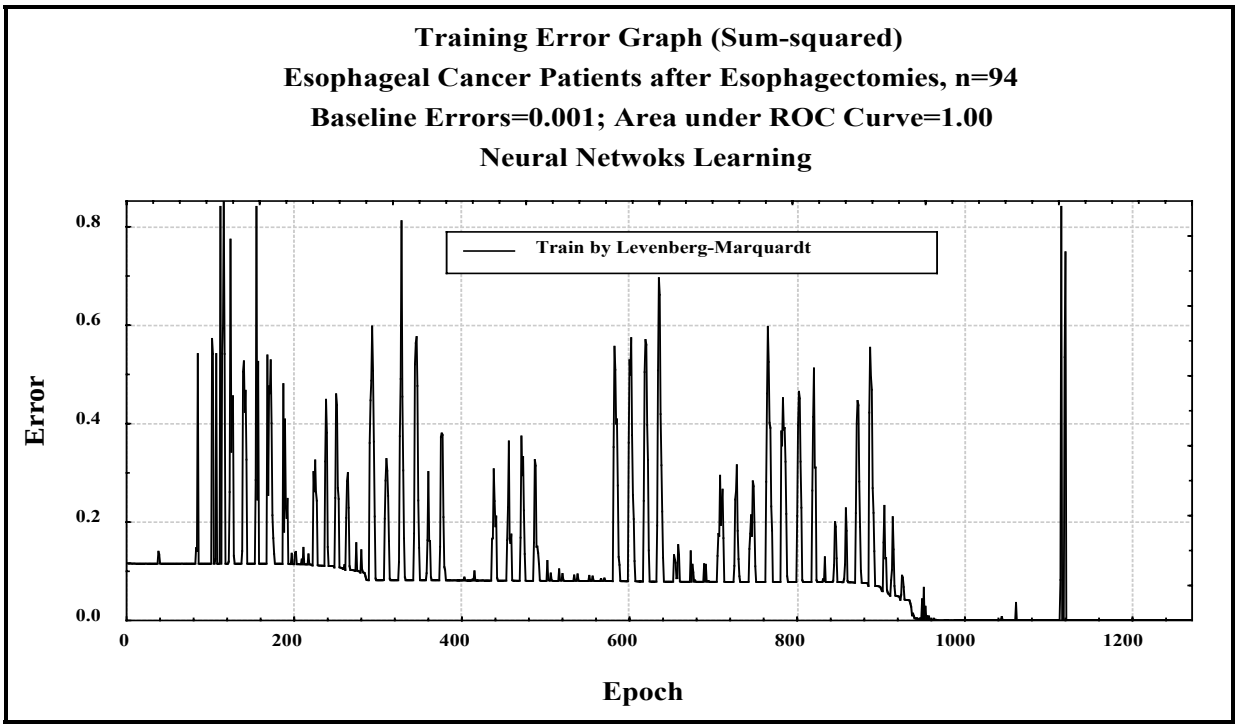

Fig. (5). Results of neural networks training in prediction of 5-year survival of ECP (n = 94; 39 5-year survivors and 55 losses): Baseline Errors = 0.001; Area under ROC Curve = 1.00; Correct Classification Rate = 100%.

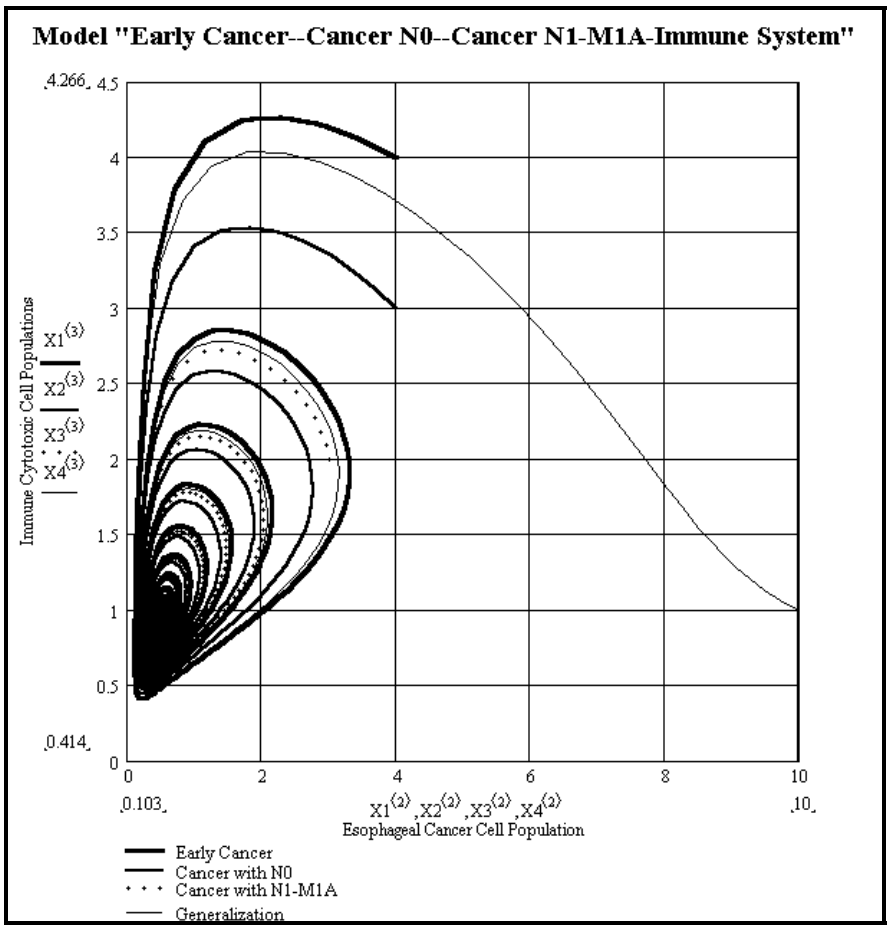

Fig. (6). Results of Holling-Tenner modeling of system "EC—Lymphocytes" in prediction of ECP survival after esophagectomies.

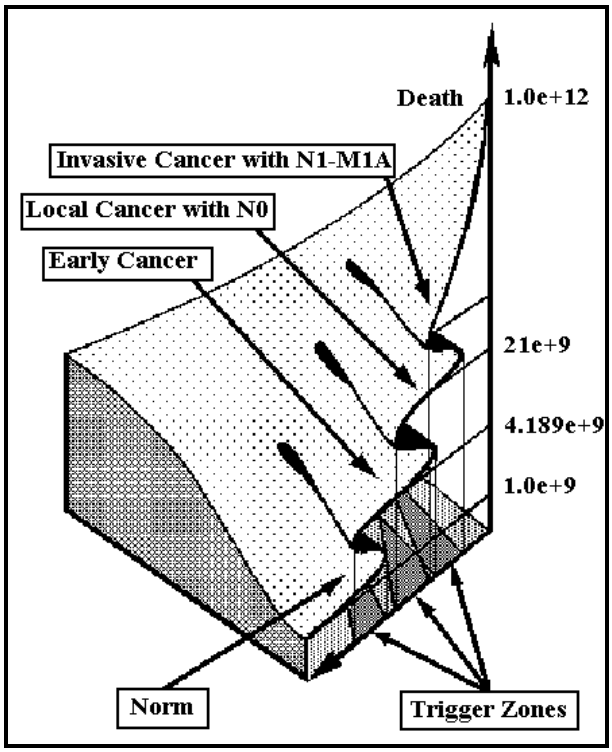

Fig. (7). Presence of the two phase transitions "early cancer—invasive cancer" and "cancer with N0—cancer with N1-M1A" in terms of synergetics.

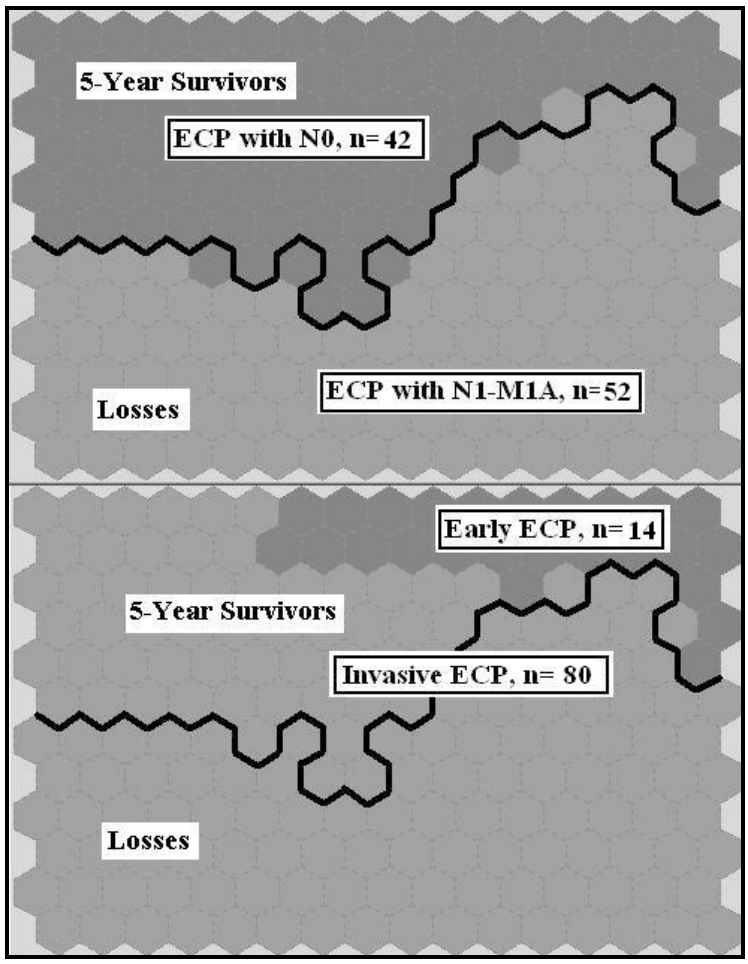

Fig. (8). Results of Kohonen self-organizing neural networks computing in prediction of ECP survival after Esophagectomies (n = 94).

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. (**9**) (Global χ^2 = 10691.5; Df = 1533; P = 0.000000; n = 94) it was revealed that the seven clusters significantly predicted 5-year survival and life span of ECP after esophagectomies: 1) phase transition "early EC—invasive EC" (P = 0.001); 2) phase transition "EC with N0—EC with N1-M1A" (P = 0.000); 3) cell ratio factors (P = 0.001); 4) EC characteristics (P = 0.000); 5) biochemical homeostasis (P = 0.000); 6) hemostasis system (P = 0.043) and 7) combined procedures and adjuvant chemoimmunoradiotherapy (P = 0.030) (Fig. **9**). It is necessary to pay attention, that both phase transitions strictly depend on blood cell circuit and cell ratio factors.

DISCUSSION

Treatment of ECP is an extremely difficult problem. On the one hand, the esophageal cancer surgery demands masterly surgical technique and always will remain the privilege of very experienced professionals [11]. 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 [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 30-35% and practically is not improved during the past 30-40 years, as the great majority of patients has already EC with stage III-IVA [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 em-

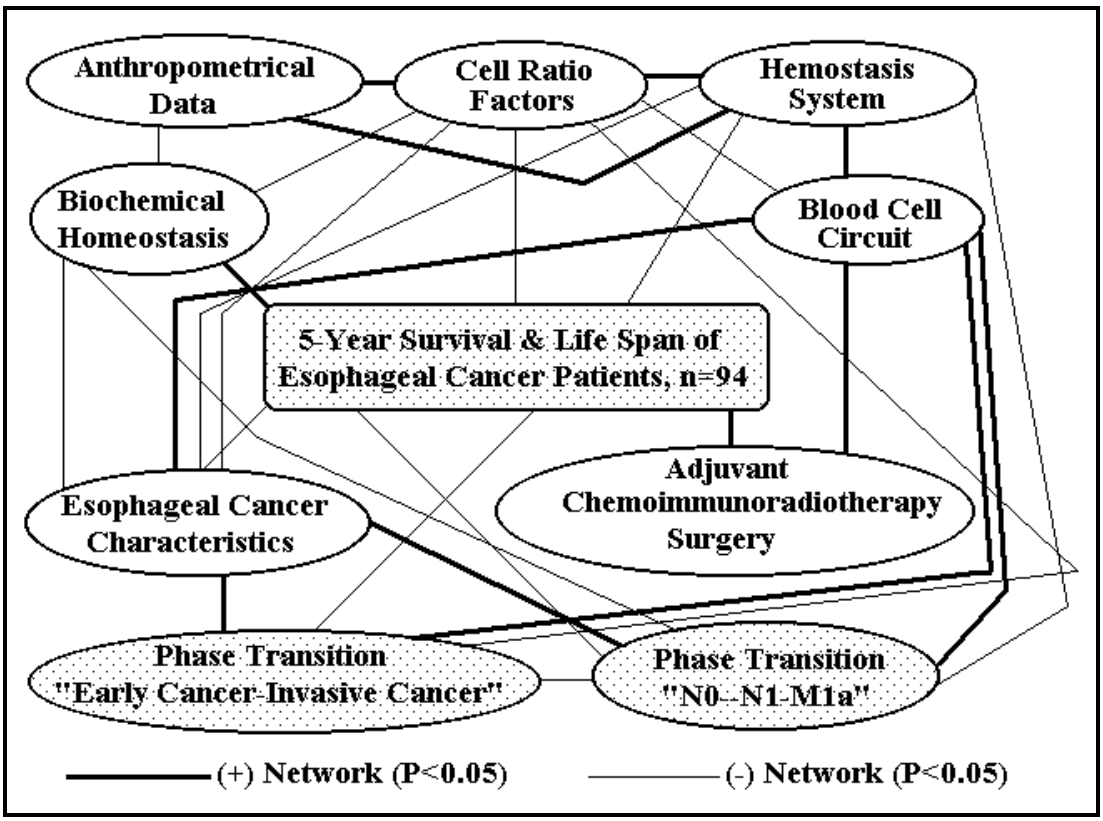

Fig. (9). Significant networks between ECP (n = 94) survival, cancer characteristics, blood cell circuit, cell ratio factors, hemostasis system, biochemic and anthropometric data, phase transition "early cancer—invasive cancer", phase transition "cancer with N0—cancer with N1-M1A" and treatment protocols (SEPATH network model).

ployed 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. [14-16]. On the other hand new immunomodulators, new adoptive immunotherapeutic modalities with lymphokineactivated 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-M1A after complete esophagectomies. Present research only confirmed this axiom.

In summary, when adjuvant chemoimmunoradiotherapy is applied to complete esophagectomies for EC with N1-M1A, 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 stage IIB-IVA 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.

In 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 lymphadenectomy for completeness; 4) precise prediction and 5) AT for ECP with unfavorable prognosis.

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