Kirkilevsky S. I., Lurín A. G., Dubinina V. G., Lukyanchuk O. V., Mashukov A. A., Bilenko A. A., Zgura A. N., Osadchy D. N., Maksimovskiy V. E. Some novel ways of gastric cancer patients treatment personification. Journal of Education, Health and Sport. 2017;7(5):516-538. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.801825
http://ojs.ukw.edu.pl/index.php/johs/article/view/4499

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26.01.2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.05.2017. Revised: 23.05.2017. Accepted: 31.05.2017.

UDK 616.33-006.6-089-085.277.3

SOME NOVEL WAYS OF GASTRIC CANCER PATIENTS TREATMENT PERSONIFICATION

S. I. Kirkilevsky[1], A. G. Lurín[3], V. G. Dubinina[2], O. V. Lukyanchuk[2,3], A. A. Mashukov[1,2,3], A. A. Bilenko[2], A. N. Zgura[3], D. N. Osadchy[2], V. E. Maksimovskiy[2]

National Cancer Institute[1], Kiev
Odessa National Medical university[2], Odessa
Odessa Regional Oncology Center[3], Odessa

Abstract

In this paper the authors perform the analysis of molecular and morphological factors influencing the survival of patients with gastric cancer (n = 221). They analyzed the survival rate in this group of patients based on the analysis of molecular markers VEGFR, p53, Her2, Ki-67. Measured role in the survival such factors as the degree of differentiation of primary gastric tumors, the presence of microscopic tumor involvement of perineural and perivascular spaces, the degree of invasion to gastric wall by T1 = 1 and to T4a = 4, T4b = 5, number of regional lymph nodes affected by metastasis, and other factors. As an arbitrator used survival curves calculated by the method of R. J. Cox, time of lifespan, measured in months, as well as a comparison of the areas under the curves of survival.

Keywords: gastric cancer (GC), lymph node dissection, multiorgan resection, immunohistochemistry, genetic classification.

Introduction

The study of survival of cancer patients is in the focus of our diligent attention in the clinical and experimental oncology. Many factors affect the quantitative and qualitative analysis of lifespan of treated patients. At the moment not aware of any tool or instrument that could measure the anticipating duration of the life expectancy of the treated individual. However, based on the mathematical analysis of many factors at once, it is possible to predict the life expectancy of patients with gastric cancer. It depends on many factors, which are variable, ie, they may vary by the influence of many factors. Our task is to follow up such trends, when knowing the patient's age, stage of disease, the exponents of aggressiveness of the tumor biology, you can make a tentative forecast duration of the forthcoming life after surgery. It does not consider the possibility of other causes of death of the patient, non-oncological disease (heart attacks, strokes, other reasons). One of the most frequently asked question is "how long lifespan you, as a doctor, can give?" The doctor did not provide the man's life, it is not in his power; but given the significant clinical experience, mathematical tools available to us today, it would be a misunderstanding at least do not try to do it. Only on the very surface are seen such factors as:

1. Cancer in younger people proceeds more aggressively, and its biology and the rate of metabolic processes, the cell cycle velocity is different from the torpid, sometimes lasting for decades cancer in the elderly

2. The stage of the tumor process is constantly changing depending on the revision of TNM classification. For instance, once it meant N1 (which is logical) affected lymph node metastases paragastrical lymph nodes; then N1 stage means the involvment from 1 to 6 regional lymph nodes by metastases, and now N1 stage naturally means only 1 or 2 lymph nodes involvment. Describing this fact in terms of figures, we can say that N1 ≠ N1 ≠ N1. A survival statistics depending on the stage tends to be unchanged, as data changes in GC TNM classification [9, 10, 21] occurred during last 10 years.

3. The degree of differentiation, G, and the number of mitosis (proliferation index Ki-67) are factors in determining the aggressiveness of tumor growth, but nowhere in the literature you will not find such a forecast. We have not seen any literature source, wherein a specific percent survival would indicate that the survival T3N1MoG1 have 40% and 30% T3N1MoG4, for example. In this age of high technology and the abundance of information on various topics in various human activity fields have not demonstrated similar statistics. In the best case, you will find some data that survival in stage I GC within 5 years tends to be 80-

90%, II stage 60-70%, III 30-40% or less, and patients in stage IV, even operated radically, cross infrequently threshold of 20% survival.

Materials and methods

Presented study was performed in the abdominal surgical department of Odessa Regional Oncology Center, included 221 patients undergoing surgery for gastric cancer in the period 2007-2013. The study was retrospective, single-center, non-randomized. The average age of 60,88 ± 10,5 years, men - 180, women - 41. In total in 143 pts performed gastrectomies and in 78 – distal subtotal resection. Gastrectomy procedure performed by Bondar method to form a loop-like anastomosis. Subtotal resection of the distal part with the formation in most cases retrocolic gastroenteroanastomosis by Billroth-2, Finsterer-Hofmeister modification.The mortality rate was 1.2%, 84% operability. It takes into account the survival of this group of patients by stages and by type of operation. Survival Analysis is shown in Table 1.

Table 1. Effect of lymphadenectomy volume on life expectancy based on the stage.

Stage of the disease	Type of lymph nodes dissection	Life expectancy months.	
1B	* D2 +	20.5 ± 8.4	p = 0.25
	D2	19.6 ± 7.5	
	D1	13.3 ± 10.64	
2	D2 +	48.0 ± 7.5	p = 0.00003
	D2	20.5 ± 12.6	
	D1	25.7 ± 12.6	
3A	D2 +	28.5 ± 5.9	p = 0.01
	D2	23.6 ± 5.9	
	D1	15.3 ± 5.9	
3B	D2 +	-	p = 0.21
	D2	13.0 ± 11.1	
	D1	22.7 ± 11.1	
4	D2 +	21.4 ± 6.0	p = 0.59
	D2	17.3 ± 6.0	
	D1	18.3 ± 6.0	

*Note: D2 +, according to modern Japanese literature on the subject indicates execution D2 dissection with simultaneous para-aortic lymphadenectomy.

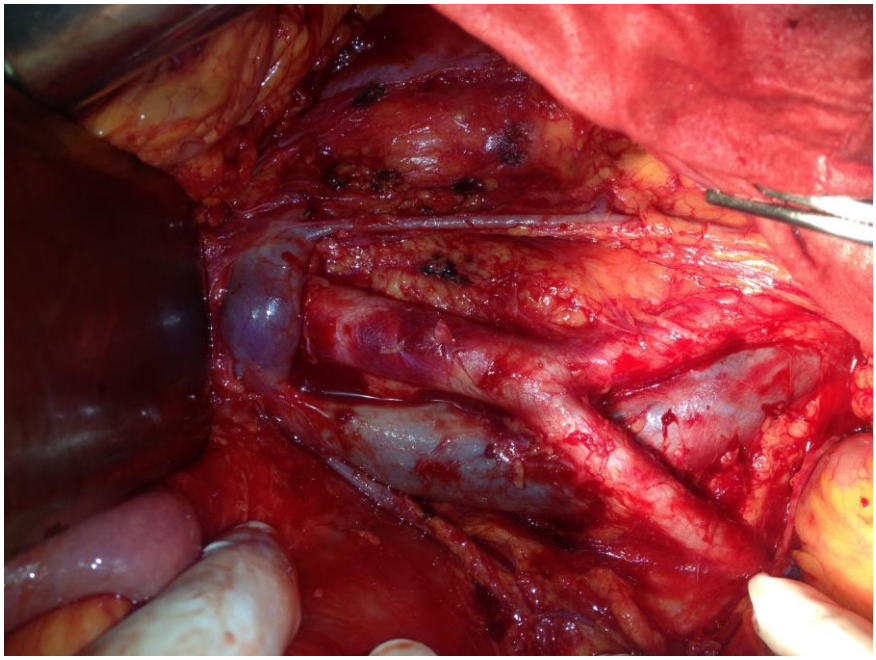


Photo 1. Intraoperative photo made para-aortic lymphadenectomy and retroperitoneal peritonectomy.

Table 2. Life expectancy measured in months, depending on the stage and type of surgery (7th revision of TNM classification).

Stage of the disease	Type of operation	Average life expectancy in the group, months.	The duration of life, depending on the type of treatment, months.
IA	Advanced \ MVR *	48	No data
	D2 lymph node dissection		48
	standard		No data
IB	Advanced \ MVR	23.5	24.7
	D2 lymph node dissection		21.8
	standard		24
II	Advanced \ MVR	34.1	48
	D2 lymph node dissection		20.3
	standard		34
IIIA	Advanced \ MVR	26.2	34.5
	D2 lymph node dissection		28.5
	standard		15.6
IIIB	Advanced \ MVR	27.5	No data
	D2 lymph node dissection		15
	standard		40
IV	Advanced \ MBVR	20.75	22.3
	D2 lymph node dissection		20.4
	standard		21.1

*MVR - multiorgan (multivisceral) resection \ gastrectomy means that resected \ removed 3 or more adjacent organs.

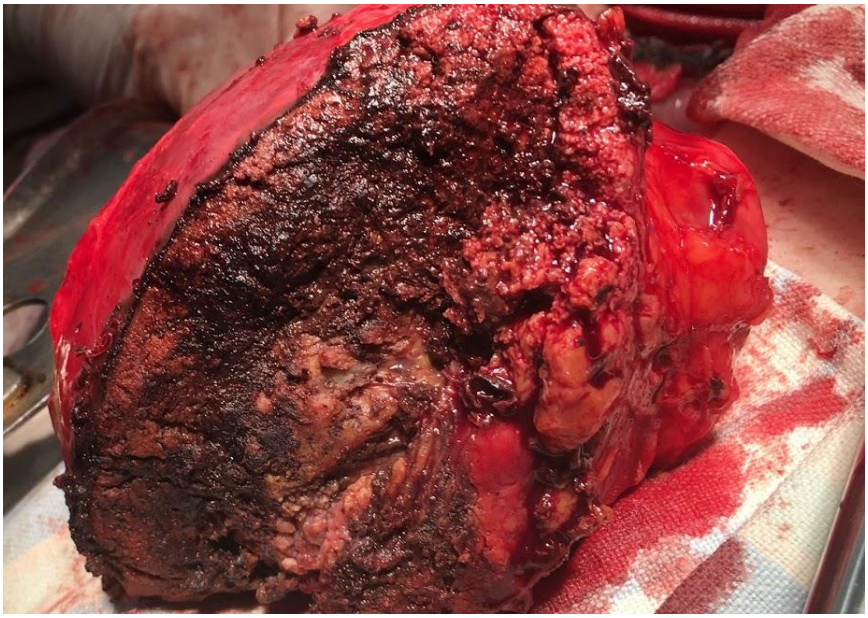


Photo 2. Component of multiorgan resection – a general view of resected liver right lobe. Resection performed using RITA technology using a specific electrode for resection of the liver, of Dr. Nagi Habib from London Hammersmith Center.

General characteristics of patients with multiorgan interventions performed is shown below. Intramural spread into esophagus registered in 31 (14.03%) patients that required resection subphrenic and, in some cases, intradiaphragmal esophageal segments. In 3 cases performed operation according to Osawa-Garlock with resection of intratoracal esophageal segment (13,58%). In 8 cases - resection of subdiaphragmatic segment by Savinyh (3.62%). Duodenum involvment - in 2 (0.91%) patients were classified morphology be the greatest depth of invasion. Pancreatic resections were performed in 44 patients (19.91%), of which the true histologicaly proofed involvement of pancreas found in 5 patients (2.26%), atypical liver resection – in 9 patients (4.07%), anatomical resection – in 3 patients (1.36%). Splenectomy performed in 153 cases (69.23%), most frequently - as component of LND + D1 and higher. In 5 cases there was detected splenic capsula metastases (2.26%). In 2 cases, the splenic gate dissection was performed as a component of splen-sparing operations (0.91%).

The life of a particular cancer patient - this is not only Story about the stage, type and extention on an adjacent structures. In the next group of prognostic determinants should be necessarily included the age of patient, tumor volume (ie number of cell colonies which do not take into account in the TNM), the degree of genetic "controllability" of the cell cycle (the severity of the expression of TP53 oncoprotein by immunohistochemical analisis - IHC) expression of neoangiogenesis VEGFR markers [11, 12, 13, 14, 15].

Table 3. The differences between expressing oncoproteins established by the authors in sole order to form the equivalent groups of patients.

	TP53	VEGFR-C	Ki-67	Her2 \ new
"Positive" reading marker	11-100%	"++" "+"	0-20%	"+" "++" "+++"
"Negative" reading marker	0-10%	«±» "-"	21-100%	"-"

Her2 \ new marker for gastric cancer is to define as a "positive" even in the case of expression "+" corresponding oncoprotein - Sheffield Brandon [26].

Table 4. Dependence of pts longevity (months) accordint to the stage, and histological type respectively.

Stage of the disease	View dissect ion	Differential-ings		The presence of tumor emboli		The presence of residual tumor tissue		The presence of perineural invasion	
		G1/G2	G3/G4	Vo	V1	Ro	R1	Nev/0	Nev/1
IA	D2 +	-	-	-	-	-	-	-	-
	D2	48	-	48	-	48	-	48	-
	D1	-	-	-	-	-	-	-	-
IB	D2 +	26.5	21	26	18	24.7	-	26	18
	D2	21	24	21	24	22.8	-	21	21
	D1	24	-	24	-	24	-	24	-
II	D2 +	-	48	-	48	48	-	-	48
	D2	27	13	24	18.5	20.3	-	37.3	24
	D1	34	-	32	24	29.3	48	29.6	-
IIIA	D2 +	24	33.8	21	36	29.6	-	48	29.6
	D2	27.3	22.1	20.8	27	25.4	13	24.5	24
	D1	13.3	17	19.6	20	17.4	3	15.6	16
IIIB	D2 +	-	-	-	-	-	-	-	-
	D2	11.3	-	11.3	24	16.3	4	11.25	24
	D1	-	40	40	-	40	4	40	-
IV	D2 +	11.8	thirty	17.7	28.3	23	34	18.6	28.9
	D2	20.9	20.2	22.4	9	19.9	22.4	20.9	-
	D1	24	25.2	19.4	20.5	21	13.5	19.6	-

*Terashima et al. [24] found that her2-positive gastric cancer has the best indicators of disease-free and overall survival compared with her2-negative.*Kim et al. [25] The study by Cox survival at different markers expression (EGFR, VEGF, VEGF-D, VEGFR-2, VEGFR-3, TGF-α, TGF-β1 and TGF-β RII) Found that VEGF-D can be used as a prognostic factor and its high expression is associated with worse overall survival of patients. Thus, along with the third immunohistochemical marker p53 (about him, or rather its protein TP53, has described above), all of them can be used as factors of prognosis, and individualization of therapy. The

combination of these types of markers have the potential of molecular typing (epigenetic) forms of stomach cancer, just as immunohistochemical markers of breast cancer help epigenetically typed breast cancer.

Results

Intriguing results on a sample of 221 patient study showed a combination of 2 or more immunohistochemical markers. Because the ultimate goal was to form a group with independent survival. This was the first step towards drawing up mosaics of genetic types of GC. Genetic types of GC have the highest potential to create groups of patients with different survival, i.e. statistically independent objects.

Table 5. The corresponding graphs given in the diagram, the percentage survival. The area under the curve represents the product of years of survival \ patients (month x number of patients) and is a more meaningful indicator than a long duration of life. Yellow color indicates the results that are indicative of further research in this area.

Duration life months.	**MVR** + D2 lymph node dissection**,%**	**MVR%**	D2 lymph node dissection**,%**
3	96.97	95.24	97.3
6	90.91	90.48	94.52
9	84.85	85.72	91.65
12	81.71	80.96	88.7
15	75.43	76.2	85,64
18	72.15	71.44	82.47
21	68.71	68.97	79.17
24	65.1	66.42	72.57
27	61.27	61.31	69.12
thirty	57.18	58.65	65.48
33	52.78	53.32	61.63
36	47,99	50,51	57.52
39	42.65	47,54	53.1
42	36.56	41,61	44.27
45	24,51	35.67	35.45
48	12.58	32.43	28.36
60	0	25.97	18.91
72		19.51	0
84		13.08	
96		6.72	
108		0	
The area under the curve of survival, S.	19760 73	26505.99	24878.1
Number of patients	**8**	**35**	**5**

An interesting idea was used to determine significant differences between survival curves not only purely numerical (p criterion, odds ratio – OR), but also visually-numeric criteria. An example of this approach is to measure the area under the curves of survival differences. The table above shows some average duration of life of patients group without regard to its population. The area under the curve is the product of life expectancy of patients on their numbers, which in our opinion are more fully reflects the degree of influence on the treatment group.

Below the graphs shows differences in survival depending on the GC varying severity immunomorphological tumor characteristics.

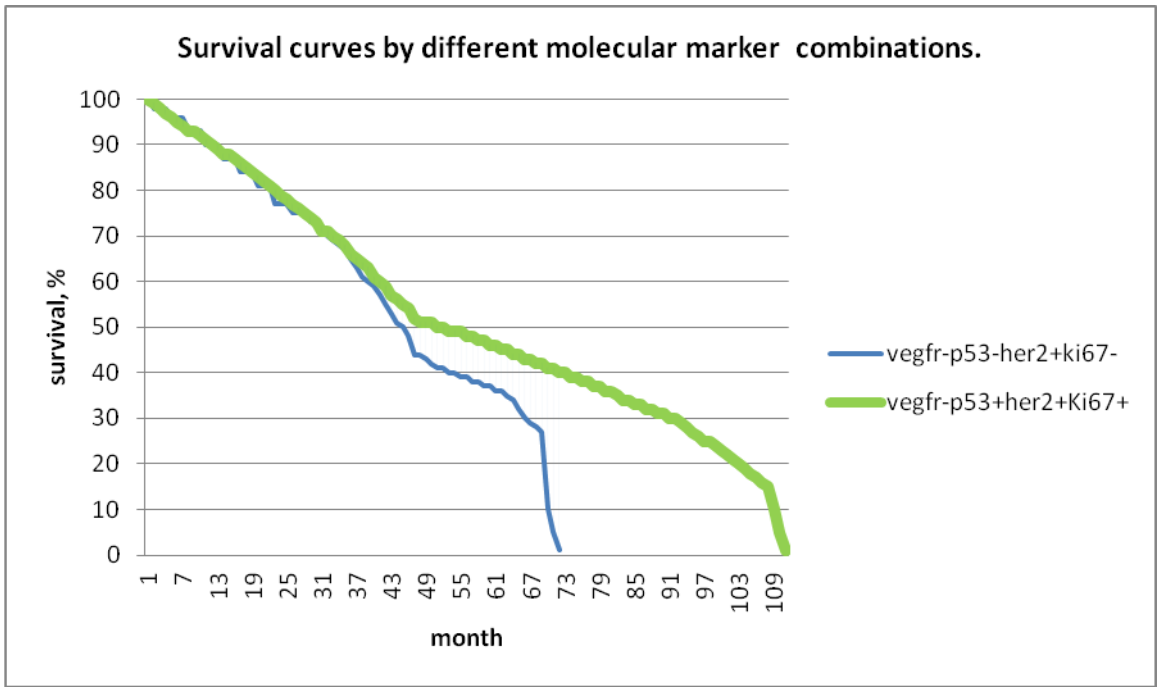


Figure 1. Survival of patients with gastric cancer with vegfr-p53-her2+ki67-set and vegfr-p53+her2+Ki67+set. P = 0.017195.Calculations were made with the help of mathematical capacity of calculators available online http://statpages.info/.

Worst prognosis of survival, focusing on a group of patients who had made up the so-called "Triple-negative" GC, in analogy to a similar form of breast cancer. It is characterized by the absence of neoangiogenesis manifestations, TP53 protein expression and lack of response to the analyzed slides immunohistochemical dyes protein c-erbB2 [3, 5, 16, 17, 18, 19, 20].

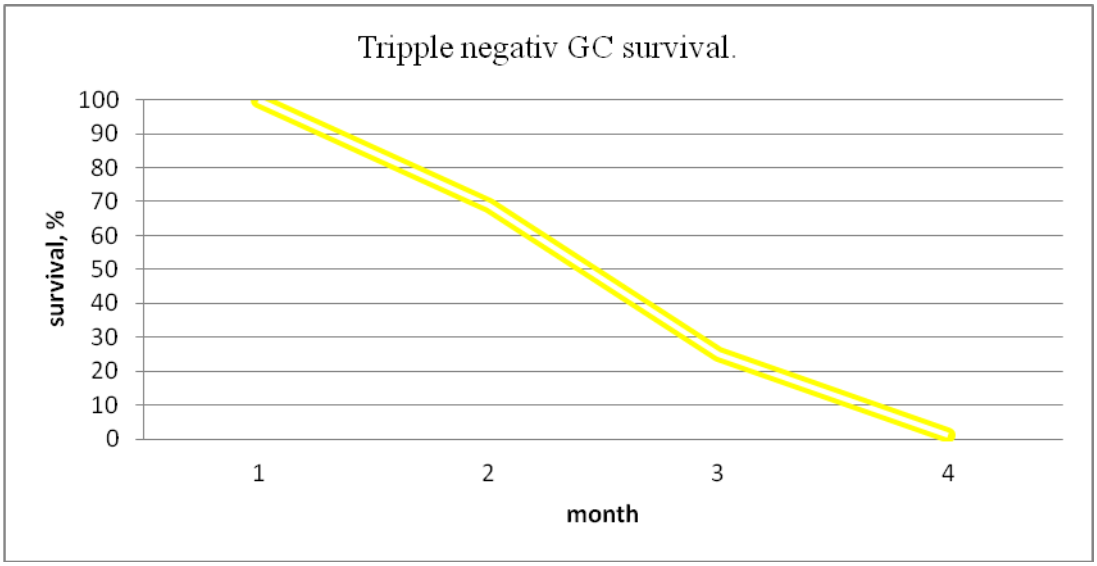


Figure 2. Graph of survival so-called "Triple negative GC" VEGFR-p53-Her2-.

An interesting feature identified during the analysis of marker combinations, VEGFR-p53-Her2+Ki-67-set were highlighted highly differentiated forms without growth into adjacent structures, exophytic growth pattern, with no signs of aggressive growth. Those what are commonly referred to as local forms, promising in terms of long-term survival even in loco-regional stage. But overall survival in this group, as shown in Fig. 4 will be comparatively low. They are is histologically "good" cancers with a "bad" IHC and thus pretty well prognosis.

Table 6 Cumulative impact on survival criteria G, V, R, Nev patients, regardless of the stage and method of dissection, months.

	G		V		R		Nev	
	G1 \ G2	G3 \ G4	Vo	V1	Ro	R1	**Nev \ 0**	Nev \ 1
The average duration of observation, months	23.8 ± 6.3	15.9 ± 6.3	23.6 ± 5.6	19.2 ± 5.6	24.7 ± 7.1	10.6 ± 7.1	24.6 ± 6.0	12.9 ± 6.0
reliability differences	p = 0.079		p = 0.25		p = 0.0075		p = 0.0092	

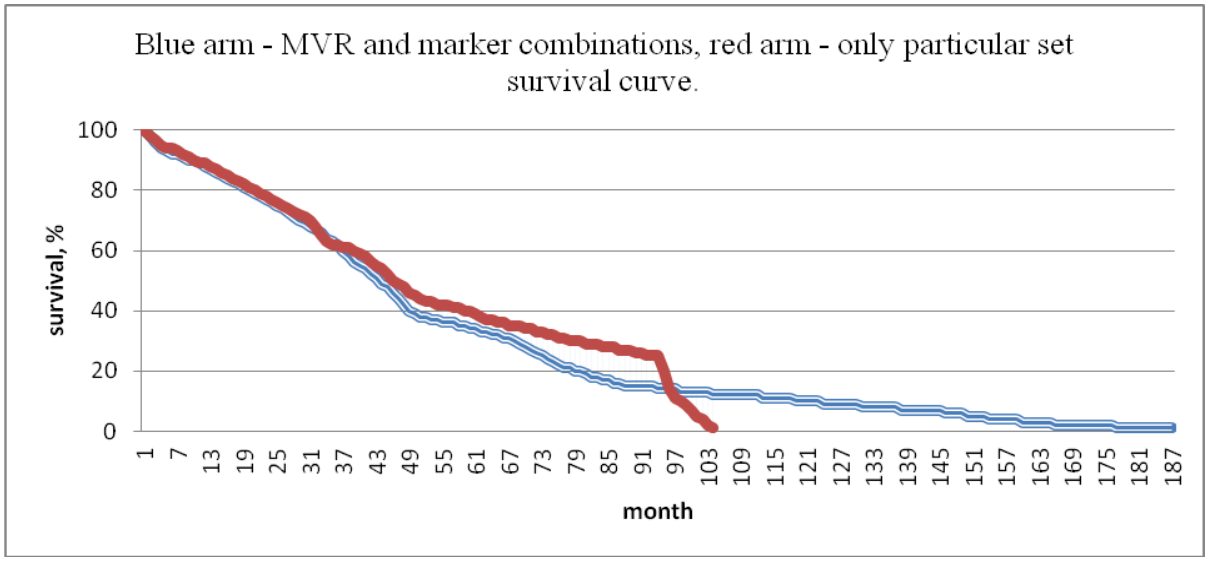
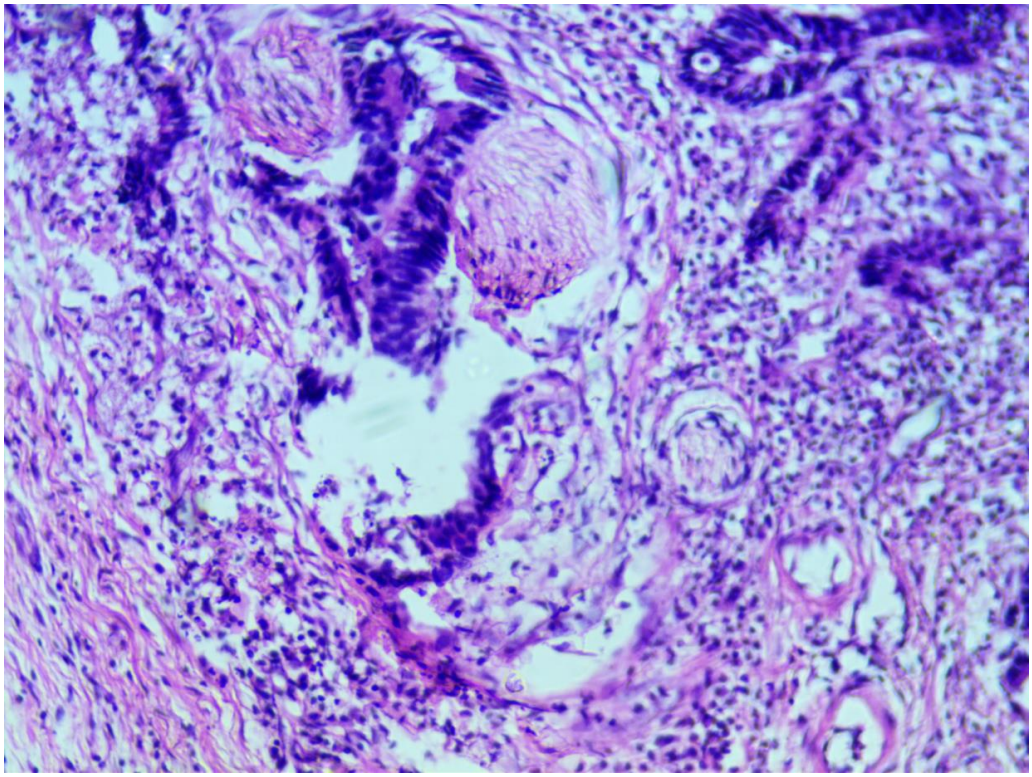


Figure 3. Visualisation of effect of multiorganic resection (MOR, MVR) on survival of patients with VEGFR-p53+Her2-Ki-67+set of markers. The group called "group of the 100th month."

Found a group where the implementation of multiorgan resections impact on survival of patients with gastric cancer in the later stages of observation - after 100 months. The main, the critical feature group VEGFR-p53+Her2-Ki-67+ was the absence of metastasis to regional lymph nodes even in the presence of T4 tumors. Why in this group were more effective MVR, and not D2 LND remains a puzzle to us.

We have recently made the conclusion: significant efficiency performance multiorgan resections in microsatellite-unstable GC [4, 6, 7, 8, 22]; mainly the absence of metastases in regional lymph nodes, as well as lack of capacity "occult" generalization, such as perineural growth.



Micrograph 1. Micrograph tumor "prominence" in the lumen of perineural stroke in the upper middle part of the microscopic picture.

The survival rate of patients with gastric cancer is the criterion that allows you to properly assess the effectiveness of any therapeutic effects, diagnostic criteria and compare the methods of diagnosis and treatment of each other. Survival is an integrative index summing the duration of life of patients in the group for the purpose of calculating the average value. The peculiarity of mathematical methods of studying the survival mechanisms is to use probability theory to predict the 5-year survival rate. Even in the early stages of the application of these techniques in medical computing - and it was the so-called survival of the table - it was possible to calculate the 5-year survival rate in a sample of patients, some of whom were treated with at least 5 years ago. Thus, the time elapsed from the time difference between the treatment and control start and end points of therapy in all treated could be different. In practice, this results in the possibility of mathematical precision greater than 95% (which is enough for biomedical observations) calculate the group overall survival of patients exposed to a particular treatment. And then compare the resulting effects (survival change) by comparing survival curves. In the event that the difference between survival curves is statistically significantly different (or $r<0,05$ $OR\geq1$), the effect of the method is recognized clinically \ diagnostically valuable. Some researchers, thus, give more importance to visually

distinguish between two curves (the so-called estimate of the area size between the curves) as a marker of the presence and authenticity of differences. There are techniques, assessing p between certain points of the two curves in their places of maximum divergence (or, another embodiment in median time points, where the number of groups is halved); others allow to calculate the significance of differences between the curves p as two mathematical sets. There is a fairly large number of methods to calculate the significance of differences p: Student's, Pearson, Mann-Whitney-Wilcoxon. As calculation techniques and imaging survival rates: Kaplan-Mayer, Cox and others.

In this sense, for example, the ability of any classification to form groups with significantly different survival rates of patients with evidence of the correctness of generated staging system. Because modern mathematical model of survival is objective, and the most perfect staging system was invented, is subjective and introduced artificially. Thus, the reliability calculation survival differences can evaluate not only the effectiveness of the treatment, but also the power of the diagnostic method. The term "group of independent survival" can be used to describe a set of survival rates of groups of patients with varying, e.g., the degree of differentiation of the primary tumor (G1-G2-G3-G4); with various primary objective tumor size (cm2); presence-absence perineural-perivascular infiltration. Finally, the most classical academic sources of differences - different localization of the tumor in the stomach.

An interesting observation is conducted by the workpiece varying the concept of "the degree of malignancy" or "degree of biological aggressiveness" depending on the combination of IHC markers. This can hardly be called staging, because due to the small size of the group we could not identify 3-4 groups in each of the VEGFR, p53, Her2, Ki-67 species. Therefore, the survival of a group seen as the Chief Arbiter of the aggressiveness of the cancer, making it a more "malignant" or, on the contrary more torpid and "benign".

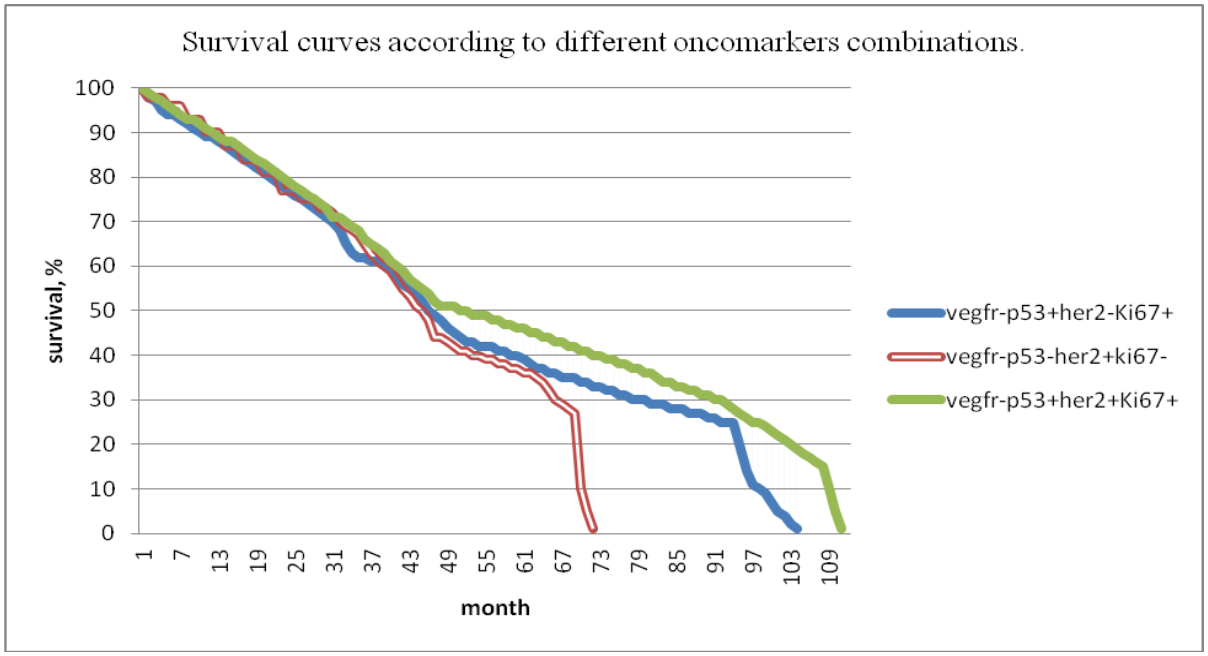


Figure 4: Graph that shows the possibility of protein markers to create groups with different survival.

Group 100 of month (blue arm) VEGFR-p53+Her2-Ki-67+ can be named group of "poor IHC set" because of the high proliferative potential Ki-67 [2], but relatively favorable prognosis.

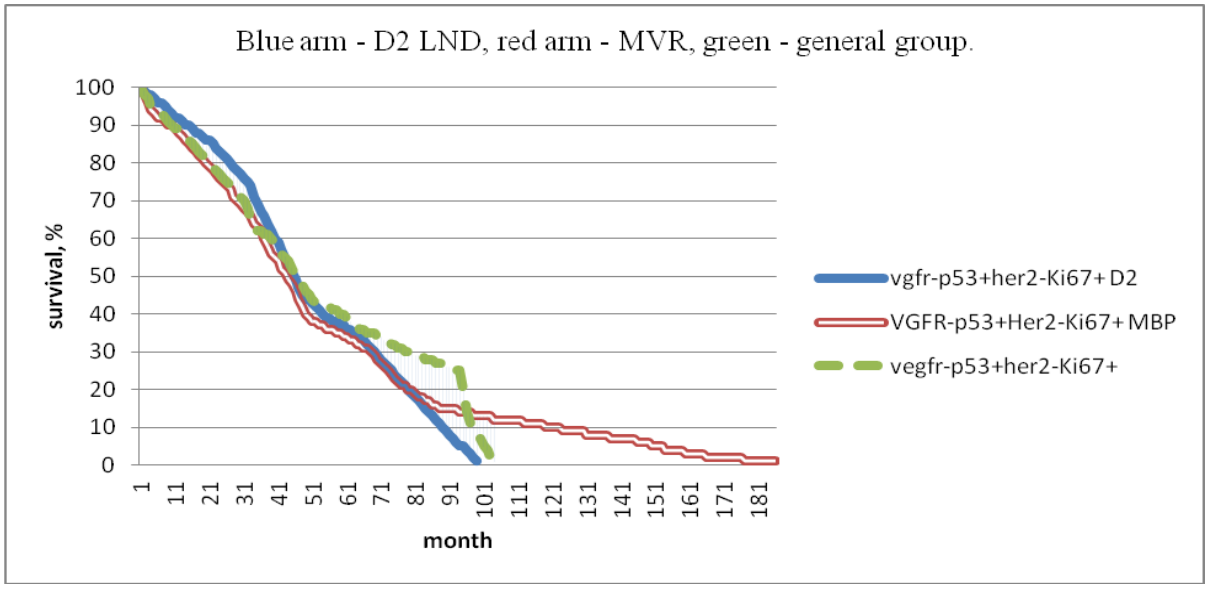


Figure 5. Charts visualising influence of D2 lymph node dissections (LND) and multiorgan resection on survival of patients with combination VEGFR-p53+Her2-Ki-67+ markers. The group called "group of the 100th month" (overall survival of the group - a green dotted line).

When we analyzed the whole group of patients with gastric cancer (n = 221), charts the survival of patients with tumors of the gastric antrum, body and cardia parts. Encouraging was to see that there exists a system of coordinates (VEGFR-p53+Her2-Ki-67+), where "antral stomachs" live longer than traditionally "bad" in terms of long-term survival of patients operated for epithelial malignancies of body tumors and cardia-located lesions.

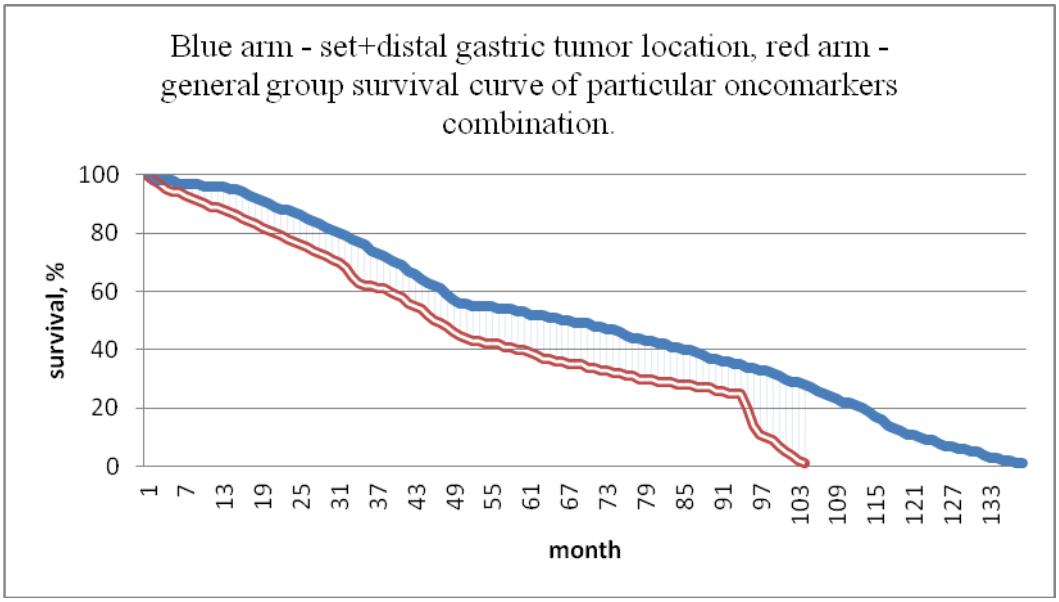


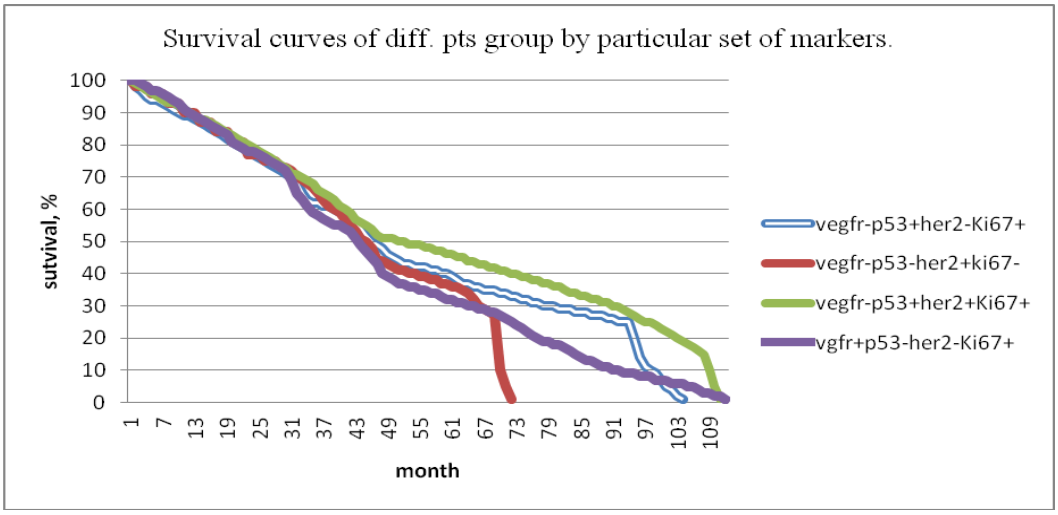
Figure 6. Influencies of localization tumor in the stomach onto survival, patients with VEGFR-p53+Her2-Ki-67+set.

Given data, the presence of the appropriate mathematical tools our capability to predict the life expectancy is acknowledged relatively high.

The meaning of the invention is to find specific digital multipliers and mathematical formulas for the prediction of the estimated life expectancy of patients with GC and, respectively, some extra insight on personalization / individualization of complex treatment options subject.

The method and formula may be used by surgeons and to personalize chemotherapeutical (her2 \ new, VEGFR) and surgical methods of individualizing treatment: depending on the invasion of the wall, the patient's age, affected lymph nodes, tumor size, tumor grade G and bioharassment p53 [1.23] .

Figure 6, which demonstrated TP53 oncoprotein expression effect on survival. The green and blue curves represent the best survival situation.



Effect of high Ki-67 proliferative index in these groups of patients (green and blue survival curves) offset the influence of p53 expression.

Detected digital values factors relevant variables and their relationships in the formula (e.g. x6 - "floating" variable, which characterizes the value concentration oncoprotein VEGFR) are the essence of the invention.

Modifier degree of differentiation = 38.57020554889854

Modifier p53 expression marker = 14.79373951516277 + x6

Modifier variable degree of wall invasion = 10.631088579592571

Modifier variable number of affected lymph nodes = -14.096156327772121

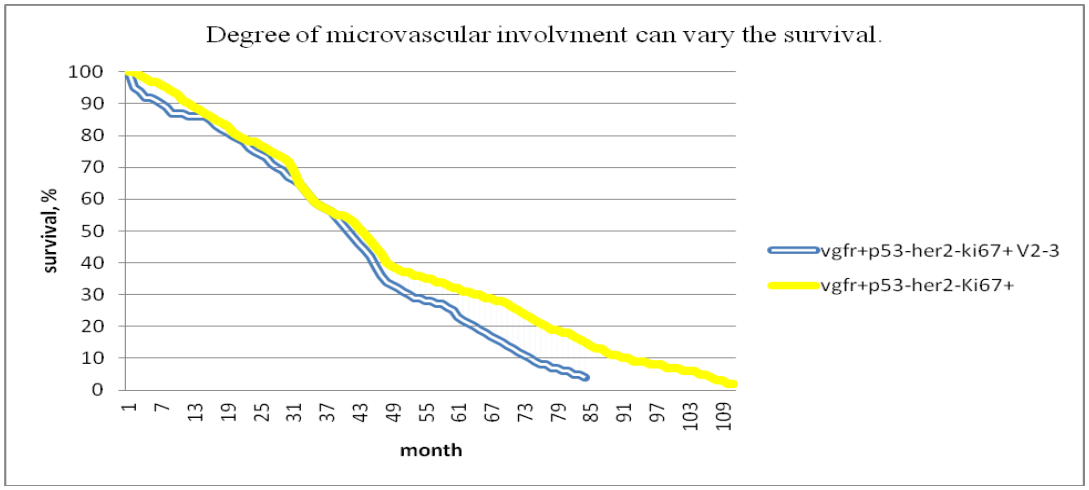
Tumor size, measured by CT = -0.37371001935662385

Variable characterizing the protein concentration her2 \ new = 2.2679620241496714

Modifier variable characterizing the estimated time of life = -1.1666992349525311

Modifier variable characterizing the protein concentration VEGFR- free variable (can be any).

Figure 7. The combination of the presence of oncoproteinVEGFR with the presence of tumor emboli in a lumen of microscopic lymph vessels (histologically look like a slit), blood (component have smooth muscle in the wall) and venous-type worsen survival.



It is difficult to say why during neoangiogenesis protein present in the tumor itself is not always GC showed tropism for microscopic spreading (not always even in the step T4, which here n = 5). Apparently, in this case, the value had high proliferative index, low indices of p53 and CD 340.

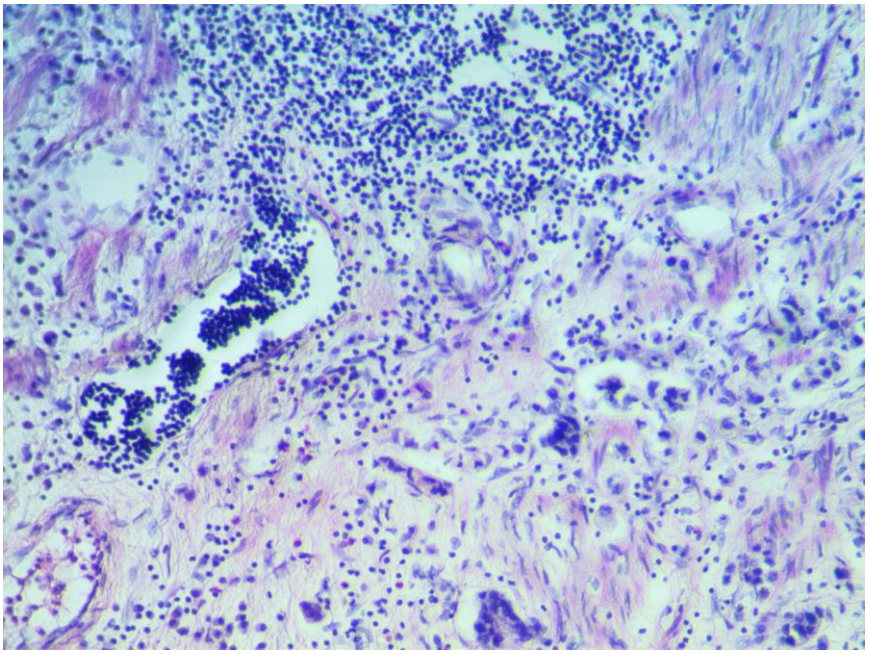
The degree of vascular (v, venous and ly, lymphatic) classified by engagement JRSGC [21]:

v0, ly0 - no vascular invasion;

v1, ly1 - minimum vascular invasion;

v2, ly2 - mild vascular invasion;

v3, ly3 - severe vascular invasion.



Micrograph 2. Tumor extravasates in the lumen of the vessel muscle-type (visible smooth muscle) in the left middle portion of the microscopic pattern.

Thus possible to track the effect of various oncoproteins biological propensity of tumor involved in microvascular own environment, create new vessels to penetrate into them and create tumor emboli circulating tumor complexes. In fact, in Mikrofot. 2 illustrates one of such migrating complexes, ready to "sail".

Table 7. Correlation between histological and immunohistochemical prediction markers in GC: tumor emboli and invasion into blood microvessels. The table shows correlations between various degrees of severity tumor vascular involvement and immunohistochemical expression of various markers.

		p53			**VEGFR-3**			**Ki67**			**Her2 \ new**		
		+		-	+		-	+		-	+		-
	Vo	52		9	67		0	88		0	13		57
	V1	9		8	0		27	0		13	0		24
	V2	20		41	14		26	50		12	12		46
	V3	31		18	0		54	12		13	13		23
Σ		112		76	81		107	150		38	38		150
R		**r<0,0001**			**r<0,0001**			**r<0,0001**			p = 0.711		
		n	95% CI		n	95% CI		n	95% CI		n	95% CI	
OR		6,452	2,776	15.411	512.071	66.910	10719,582	53.935	7.619	1084.591	0.848	0,376	1,899
Sensitivity.		0.464	0.409	0.503	0.827	0,774	0.839	0.587	0,560	0.587	0.342	0.209	0,496
Spec.		0.882	0,800	0.938	0.991	0.951	1,000	1,000	0.893	1,000	0,620	0.586	0.659
PPV		0.852	0,751	0.923	0,985	0.922	0,999	1,000	0.954	1,000	0,186	0,114	0.269
NPV		0.528	0,479	0.562	0.884	0.849	0.892	0,380	0,339	0,380	0.788	0.745	0.838
PLR		3,921	2,049	8.164	89.333	15.867	1728.203	22.88	3,935	442.038	0,900	0.506	1,453
NLR		0,608	0,530	0.738	0.174	0.161	0,237	0,424	0.408	0.516	1,061	0.765	1,348

OR - odds ratio, PPV - positive predictive value. NPV - negative predictive value. PLR - positive likelihood ratio. NLR - negative likelihood ratio.

Table 8. Evaluation of correlation depending lifespan of histological factors prognosis in gastric cancer.

The degree of correlation	numerical range Pearson coefficient values	The combination of prognostic factors
Very weak correlation	0-0.2	Stage \ perineural growth stage \ grade, stage \ absence of perivasal invasion
weak correlation	0,21-0,5	perivasal invasion \ grade, perivasal invasion \ perineural growth
The average correlation	0,51-0,7	no
high correlation	0,71-0,9	Residual disease \ perivasal invasion residual disease \ G
Very high correlation	0,91-1	Perineurium. growth \ G differentiation Perineurium. growth \ The residual microscopyical disease

The claims COUNTING projected SURVIVAL:

$$month = \frac{38.6G + (14.8 + x)p53 + 10.6T - 14.1N - 0.37S + x * VEGFR - 2.27her2}{1.17}$$

Where: G-degree of differentiation of gastric tumor. p53-positive or negative expression of TP53 oncoprotein. T-degree stomach wall involvment T1 = 1 and = 4 to T4a, T4b = 5. N-number of regional lymph nodes in which metastasis found. S-tumor area measured by CT or before surgery, or after removal of the drug pathologist. X-«floating variable». Her2-positive or negative expression of the corresponding oncoprotein. Month-approximate (estimated) life expectancy, measured in months.

Example:

[38.6 * 2 + (14.8 + 1) + 10.6 * 4-14.1 * 5-0.37 * 20-2.27] /1.17=46,35 months.

Gauss' method was used to solve the system of linear equations, variables and factors which make up the primary material studied in author`s thesis.

(Details - http://mashukov2017.livejournal.com/763.html)

Skipping more than 20 counting the steps, in order not to load readers' attention to the amount of calculations, we obtain the final step and the resulting variable factors G, x, p53, T, N, S, VEGFR, her2, month.

Subtract the seventh row of the 6th row and restored its

number	X1	X2	X3	X4	X5	X6	X7	X8	b
1	1	0	0	0	0	0	0	0	38.57020554889854
2	0	1	0	0	0	-1	0	0	14.79373951516277
3	0	0	1	0	0	0	0	0	10.631088579592571
4	0	0	0	1	0	0	0	0	-14.096156327772121
5	0	0	0	0	1	0	0	0	-0.37371001935662385
6	0	0	0	0	0	0	1	0	2.2679620241496714
7	0	0	0	0	0	0	0	1	-1.1666992349525311

Answer:

x1 = 38.57020554889854

x2 = 14.79373951516277 + x6

x3 = 10.631088579592571

x4 = -14.096156327772121

x5 = -0.37371001935662385

x7 = 2.2679620241496714

x8 = -1.1666992349525311

x6- free

Discussion

Of considerable interest is the relationship between encountered two key factors immunohistochemical factors TP53 and VEGFR: x2 = 14.79373951516277 + x6.

Thus, the obtained factors that need to multiply the variables already known for survival values obtained in the routine practice of the abdominal oncosurgical department of Odessa Regional Oncological Center. The results obtained by experimentation using an existing mathematical tools available online.

For example, https://www.symbolab.com/solver/system-of-equations-calculator.

For a more compact form, available numeric values to 17 characters after the decimal point have been rounded up to 2-3 decimal places, which is sufficient for biomedical research. Research and the very essence of his decision has nothing to do with an attempt to accurately forecast the fate of cancer patients. There is no way to know the number of days, minutes and seconds of human life God provided. For different cancer sites there is a very specific information on the survival of patients in stages of the disease. There is now a substantial need for the possession of such background information for more specific clinical situations (the number of lymph nodes get involved, tumor volume, etc.). There must be solutions that can then be used as a consultative reference information for the patient, his family, planning the number of cycles of chemotherapy, the degree of aggressiveness of complex treatment, given the expencive chemo medication, etc. Such motivation can play a role in the personalization\ individualization of therapeutic approaches.

Survival, as has been repeatedly emphasized, is ts "Arbiter", proving the bright light on the effectiveness of the treatment modality or particular diagnostic test. Quality of life, no matter how beautiful it may be, never outweighs the importance of longevity. And no matter

how perfect the questionnaire, His Majesty the Time measured in seconds, minutes, hours, days, weeks, months, years of life will always be more objective criterion. As the most credible witness to the effectiveness of therapy.

Conclusions

1. Given the high awareness of patients and their relatives, and the growing dependence of the medical community of the total availability of medical information on various topics, there is an ongoing need for a more precise gradation dependency of survival of cancer patients from different clinical and morphological situations.

2. Available mathematical, computer hardware and software tools becoming increasingly available to the practitioner who does not have special mathematical education.

3. The results will always be purely advisory, reference, recommendation, as human life can not be measured using the most sophisticated mathematics and lies outside the limits of natural computing.

4. Personification \ individualization of treatment regimens must contain some mathematical algorithms with many variables in order to provide affordable health care prognosis for the public community.

5. This paper is an attempt to provide fairly detailed report to the main questions asked by patients and their relatives; and sheds some light on the possible creation of such available systems scientometric accurate analysis applicable for various severe diseases management.

References

1. Amato M, Perrone G, Righi D, Pellegrini C, Rabitti C, Di Matteo F, Crucitti P, Caputo D, Coppola R, Tonini G, Santini D, Onetti Muda A. HER2 Status in Gastric Cancer: Comparison between Primary and Distant Metastatic Disease.Pathol Oncol Res. 2016 Jun 30. PMID: 27363700.

2. Huang G, Chen S, Wang D, Wang R, Lin L, Chen S, Wang L, Huang Q. High Ki67 Expression has Prognostic Value in Surgically-Resected T3 Gastric Adenocarcinoma.Clin Lab. 2016; 62 (1-2): 141-53. PMID: 27012044.

3. Kanayama K, Imai H, Yoneda M, Hirokawa YS, Shiraishi T. Significant intratumoral heterogeneity of human epidermal growth factor receptor 2 status in gastric cancer: A comparative study of immunohistochemistry, FISH, and dual-color in situ hybridization.Cancer Sci. 2016 Apr; 107 (4): 536-42. doi: 10.1111 / cas.12886. Epub 2016 Feb 19. PMID: 26752196.

4. Chen T, Xu XY, Zhou PH. Emerging molecular classifications and therapeutic implications for gastric cancer.Chin J Cancer. 2016 May 27; 35 (1): 49. doi: 10.1186 / s40880-016-0111-5. Review. PMID: 27233623.

5. Stahl P, Seeschaaf C, Lebok P, Kutup A, Bockhorn M, Izbicki JR, et al. Heterogeneity of amplification of HER2, EGFR, CCND1 and MYC in gastric cancer. BMC Gastroenterol. 2015; 15: 7. doi: 10.1186 / s12876-015-0231-4.

6. Zhang W. TCGA divides gastric cancer into four molecular subtypes: implications for individualized therapeutics. Chin J Cancer. 2014; 33 (10): 469-470.

7. Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. Gastroenterology. 2009; 137 (3): 824-833.

8. Burke AP, Yen TS, Shekitka KM, Sobin LH. Lymphoepithelial carcinoma of the stomach with Epstein-Barr virus demonstrated by polymerase chain reaction. Mod Pathol. 1990; 3 (3): 377-380.

9. Cidon EU, Ellis SG, Inam Y, Adeleke S, Zarif S, Geldart T. Molecular targeted agents for gastric cancer: a step forward towards personalized therapy. Cancers (Basel) 2013; 5 (1): 64-91. doi: 10.3390 / cancers5010064.

10. Jong Gwang Kim. Molecular targeted therapy for advanced gastric cancer. Korean J Intern Med. 2013 Mar; 28 (2): 149-155. PMCID: PMC3604602.

11. Tsai HL, Lin CH, Huang CW, Yang IP, Yeh YS, Hsu WH, Wu JY, Kuo CH, Tseng FY, Wang JY. Decreased peritherapeutic VEGF expression could be a predictor of responsiveness to first-line FOLFIRI plus bevacizumab in mCRC patients. Int J Clin Exp Pathol. 2015 Feb 1; 8 (2): 1900-10.

12. Weiguo Cao, Rong Fan, Weiping Yang, Yunlin Wu. VEGF-C expression is associated with the poor survival in gastric cancer tissue. Tumor Biology. April 2014, Volume 35, Issue 4, pp 3377-3383.

13. Hong-Feng Gou, Xin-Chuan Chen, Jiang Zhu, Ming Jiang, Yu Yang, Dan Cao, and Mei Hou. Expressions of COX-2 and VEGF-C in gastric cancer: correlations with lymphangiogenesis and prognostic implications. J Exp Clin Cancer Res. in 2011; 30 (1): 14. PMCID: PMC3037339 (full text).

14. Makoto Ishikawa, Joji Kitayama, Shinsuke Kazama and Hirokazu Nagawa. Expression of Vascular Endothelial Growth Factor C and D (VEGF-C and -D) is an Important Risk Factor for Lymphatic Metastasis in Undifferentiated Early Gastric Carcinoma. Japanese Journal of Clinical Oncology. Volume 33, Issue 1. Pp. 21-27 (full text).

15. Yutaka Yonemura, Yoshio Endo, Kayoko Tabata, Taiichi Kawamura, Hyo-Yung Yun, Etsurou Bandou, Takuma Sasaki, Masahiro Miura. Role of VEGF-C and VEGF-D in lymphangiogenesis in gastric cancer. International Journal of Clinical Oncology. October 2005, Volume 10, Issue 5, pp 318-327.

16. Julian Ananiev, Maya Gulubova, Irena Manolova, Georgi Tchernev. Prognostic significance of HER2 / neu expression in gastric cancer. Article (PDF Available) in Wiener klinische Wochenschrift 123 (13-14): 450-4 · July 2011 (full text).

17. Jan Trøst Jørgensen, Maria Hersom. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. J Cancer 2012; 3: 137-144. doi: 10.7150 / jca.4090 (full text).

18. C. Gravalos; A. Jimeno. HER2 in Gastric Cancer: A New Prognostic Factor and a Novel Therapeutic Target. Ann Oncol. 2008; 19 (9): 1523-1529 (full text).

19. Josef Rüschoff, Wedad Hanna, Michael Bilous, Manfred Hofmann, Robert Y Osamura, Frédérique Penault-Llorca, Marc van de Vijver and Giuseppe Viale. HER2 testing in gastric cancer: a practical approach. Modern Pathology (2012) 25, 637-650.

20. Sheffield BS1, Garratt J, Kalloger SE, Li-Chang HH, Torlakovic EE, Gilks CB, Schaeffer DF. HER2 / neu testing in gastric cancer by immunohistochemistry: assessment of interlaboratory variation. Arch Pathol Lab Med. 2014 Nov; 138 (11): 1495-502. doi: 10.5858 / arpa.2013-0604-OA.

21. Japanese Classification of Gastric Carcinoma - 2nd English Edition - Japanese Gastric Cancer Association. Gastric Cancer (1998) 1: 10-24

22. Alessandro Lugli, Inti Zlobec, Gad Singer, Andrea Kopp Lugli, Luigi M Terracciano and Robert M Genta *. Napoleon Bonaparte's gastric cancer: a clinicopathologic approach to staging, pathogenesis, and etiology. Nature Clinical Practice Gastroenterology & Hepatology (2007) 4, 52-57.

23. Kawata S, Yashima K, Yamamoto S, Sasaki S, Takeda Y, Hayashi A, Matsumoto K, Kawaguchi K, Harada K, Murawaki Y. AID (activation-induced cytidine deaminase), p53 and MLH1 expression in early gastric neoplasms and the correlation with the background mucosa. Oncol Lett. 2015 Aug; 10 (2): 737-743.

24. Terashima M, Kitada K, Ochiai A, et al. ACTS-GC Group. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II / III gastric cancer. Clin Cancer Res. 2012; 18: 5992-6000. doi: 10.1158 / 1078-0432.CCR-12-1318. [PubMed] [Cross Ref]

25. Kim JY, Jeon TJ, Bae BN, et al. The prognostic significance of growth factors and growth factor receptors in gastric adenocarcinoma. APMIS. 2013; 121: 95-104. doi: 10.1111 / j.1600-0463.2012.02942.x. [PubMed] [Cross Ref]

26. **Sheffield Brandon**, Garratt J, Kalloger SE, Li-Chang HH, Torlakovic EE, Gilks CB, Schaeffer DF. HER2 / neu testing in gastric cancer by immunohistochemistry: assessment of interlaboratory variation. Arch Pathol Lab Med. 2014 Nov; 138 (11): 1495-502. doi: 10.5858 / arpa.2013-0604-OA.