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NOVEL DATA ACCORDING WILL ROGER`S PHENOMENON IN STOMACH CANCER PATIENTS

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Summary

Mostly **Will Roger`s** phenomenon means existence of so-called "jumping" or "jumping over the stages" regional metastases in the stomach cancer patients. N1 in the 6th edition means 16 regional lymph nodes involvement, while the N1 seventh edition – only 1-2 of regional lymph nodes involvement. This means that T1N1Mo \ 6th and T1N1Mo \ 7th - not quite the same, and the survival of the two groups will be different. The study, made on the abdominal oncosurgical department of Odessa Regional Oncology Center, included 188 patients operated for gastric cancer in the period 2007-2011. The study included only radically treated patients. Comparison of survival in patients with gastric cancer between 6th revision groups of 7th has been reviewed. The classification mission is to provide differences in the survival rates between the groups.
Regression multivariate Cox analysis showed that 7th UICC classification showed different capability of stratifying survival groups of UICC N classification (P \ 0.01).

Key words: extended lymphatic dissection, TNM classification, Will Roger`s phenomenon, stomach cancer.

Introduction

Mostly **Will Roger`s** phenomenon means existence of so-called "jumping" or "jumping over the stages" regional metastases in the stomach cancer patients. For example, sentinel lymph node biopsy in the breast cancer, extended lymphatic dissection is considered inadvisable in the case of negative pathological report of removed sentinel lymphatic collector. Thus Holsted`s conception dominates: cancer cells dissemination along those lymphatic collectors occures gradually and consistently. The missing of the coming lymphatic step or barrier does not take place, tumor cells must initially fully handle the previous metastatic niche, in order to prepare the following and move farther. The next locoregional site cannot be affected, if the previous is not still completely mastered. The same is correct for some other type of malignant tumors, e.g., skin melanoma.

In medical literature 4 common directions of lymphogenic cancer dissemination are distinguished (Melnikov A.V., 1960), each of those has also for 4 steps of development:

1st direction - the outflow of lymph takes place from greater curvature of pyloric part, and its front and back walls. Steps: a) gastrocolic ligament; b) retropyloric lymph nodes; c) mesentery of initial part of small bowel; d) paraaortal lymph nodes;

2nd direction is the outflow of lymphatic liquid from lesser curvature of pyloric part of stomach and close front and back walls. Stages: on lesser curvature - a) throughout right gastric artery - b) hepato-duodenal ligament; c) hillus of liver - d) lymph nodes, directly into a liver`s hillus;

3rd direction includes outflow of lymph from the body of stomach, cardiac part of minor curvature, medial part of stomach. Stages: a) omentum minor - b) gastro-pancreatic ligament - c) extraperitoneal upper pancreatic and paraaortal lymph nodes - d) mediastinum and periesophageal lymph nodes above diaphragm;

4th direction includes outflow of lymph from the vertical part of greater curvature, its front and back walls, considerable part of stomach fundal part. Stages: a) gastro-colic ligament - b) gastro-lienal ligament - c) gate of spleen - d) spleen.

Existence of the phenomenon of "jumping" stomach cancer metastases is well-proven by many researchers [1,2] and does the biopsy of sentinel lymph node ineffective. Therefore the first place takes not the sentinel lymphatic node identification but implementation of prophylactic biopsy as possible wide amount of near-by lymphatic nodes, prophylactic lymphatic dissection.

It is, therefore, considered that removal less than 16 lymph nodes provides incorrect staging. Adequate staging might be improper even in the case of proper dissection (D2), by reason of mathematical law – Will Rodger's phenomenon [1,2], that in the appliance to the stomach cancer means the presence of "springing" or "jumping" over one of the stages regional metastases.

Interestingly, that initially the phenomenon of Will Rodger's had no attitude toward migration of the stage and to medicine in general, and touched a seeming paradox (focus), consisting in that transferring (numeral) of element from one great number in other can increase the mean value of both great numbers.

For the best illustration of this widespread phenomenon we will consider two great numbers, X and Y :

X = {1, 2, 3, 4},

Y = {**5**, 6, 7, 8, 9}.

Arithmetic sum of elements of X is equal to elements of Y = 7.

However, if number 5 to transfer from X in Y, getting

X = {1, 2, 3, 4, **5**},

Y = {6, 7, 8, 9},

the calculation that mean value of elements of X will rise to 3, and mean value of elements of Y - to 7,5.

Image 1. Will Rodger has an authorship of so well-known in biology phenomenon.

Because these people are not healthy, removing them from the set of healthy people increases the average lifespan of the healthy group. Likewise, the migrated people are healthier than the people already in the unhealthy set, so adding them raises the average lifespan of that group as well. Both lifespans are statistically lengthened, even if early detection of a cancer does not lead to better treatment: because it is detected earlier, more time is lived in the "unhealthy" set of people. Adding of them to the great number promotes the middle index of health [1]. Classification of the same group of oncologic patients simultaneously according 6th and 7th variants of revision of classification of TNM appropriately will cause the outflow of part of patients from one stage into other. And that, in turn, is able to change the indexes of survivability the same, it would seem, groups of patients.

Background

Thus, Sumin Chae et al. compared the efficacy of 7th TNM classification in comparison with the 5th \ 6th, as a factor in the prognosis of gastric cancer. It is concluded that the number of affected lymph nodes is a major prognostic factor. The study was conducted to assess the rationality of [7] 7th revision of the International Classification comparison with 6th classification. Analyzed 295 patients included in the study for four years. In accordance with the seventh edition of the UICC, N classification, 5-year cumulative survival for N0, N1, N2, N3a and N3b totaled 89.7, 73.6, 54.9, 23.1 and 5.4%, respectively (P \ 0.0001). Using univariate analysis, it was concluded that the N classification of the seventh and sixth UICC / AJCC

TNM staging system, T-seventh classification of UICC TNM staging system, the size and location of the tumor, as well as histology, were significantly associated with overall survival for gastric cancer. At the same time, regression multivariate Cox analysis showed that 7th UICC N classification was an independent prognostic factor instead of six UICC N classification (P \ 0.0001).

N1 in the 6th edition means 16 regional lymph nodes involvement, while the N1 seventh edition – only 1-2 of regional lymph nodes involvement. This means that T1N1Mo \ 6th and T1N1Mo \ 7th - not quite the same, and the survival of the two groups will be different. This group of patients previously classified as now will be in a different stage of the disease and thus shifts the statistics of the stage. These are the "Okies" of Will Roger who moved from Oklahoma to California:

N1 \6th edition: ⟶ { N1 \7th edition; N2 \7th edition }

Thus, summing up the results of a point, we can say that studying phenomenon exists as if in three dimensions, three senses. In the conventional sense it means those jumping, biologically aggressive "penetrating" metastases. In a wider sense - it transfers patients from one to another stage of the classification while changing the method of describtion. And here and there "okies" Will Roger moved from Oklahoma to California, and vice versa.

Firstly, it is certainly a great example of how imperfect staging system for cancer in general, and particularly for stomach cancer. "Jumping" (better translated "skipping") lymphotropic metastasis, leading to heterogeneous description of the criteria N, and therefore does not fulfill adequate volume of lymph node dissection and further therapy. Although who is #1 in this case - the chicken or the egg - inadequate staging or a selected volume of lymphatic dissection?

Secondly, the very trick of W. Roger, of course, is contrary to the experience of the observer. Since the transfer of at least one number from one group to another leads to a change in all group`s calculations. It increases the numeric value of the average of both sets, which means a change of the standard deviation or median survival.

Finally, in the third. This phenomenon shows the importance of the proper distribution of values in the group (i.e. stratification). Because each subsequent new (5th, 6th, 7th, 8th expect) TNM classification attempts to stratify gastric cancer patients very differently. Compare staged according to the different understanding of the TNM classification in the meta-analyzes can be carried out incorrectly.

Sir Robert Maldon, one of the historically known Prime Minister of New Zealand, is famous for the phrase "New Zealanders are immigrating to Australia, increase the IQ of both countries." The migration of patients to another stage when a classification system has been changed is a really existing event; particularly Daniele Marrelli called it “shift” stage [4].

Talking about the phenomenon of migration of patients from stage to stage at different classification of the same group, we should make a literary reference.

Shiro Kikuchi et al. [6] studied 609 patients with advanced gastric cancer who underwent extended lymphadenectomy. 7th compares the effectiveness of the TNM classification in comparison with the 6th classification as a factor in the prognosis of gastric cancer. 5-year survival rate showed no difference in survival: IB 88%; II74%; IIIA 53%; IIIB 39%; and IV 18% (IIIA versus IIIB, p = 0.1307) for the TNM VI edition; IB 94%; IIA 85%; IIB 71%; IIIA 68%; IIIB 48%; IIIC 23%; and IV 13%; (IIB against IIIA, p = 0.7665; IIIC against IV, p = 0.4156) for the seventh and TNM JCGC 14th edition; N0 85%; N1 70%; 46% N2; N3 18%; M1 and 13%; (N3 against M1, p = 0.8640) for the sixth edition of TNM; N0 and 85%; N1 80%; 61% N2; N3a 46%; N3b 18%; M1 and 13%; (N0 vs. N1, p = 0.2735; N2 against N3a, p = 0.0663; N3b against M1, p = 0.8640) for the seventh and JCGC 14 edition. It is concluded that the classification of patients by TNM JCGC seventh and the 14th edition is not always superior to TNM 6th edition to determine the prognosis after radical surgery in advanced stage of gastric cancer. Extended lymph node dissection can be effective for N0-N3a, but not for N3b and M1 are TNM stages 7th edition and JCGC 14th edition.

In our study, the migration of subgroups of patients with gastric cancer from one stage to another, due to the change of the descriptive system of staging, led to a decrease in the risk of death by 17% for the second stage and 55% - for the third. Compare life expectancy of patients with gastric cancer in groups T4aN3aM0 (described by a former version like T3N2M0) and T4bN3M0 (in 6th - T4N2M0) stages revealed significant differences in survival. Significant differences were respectively p = 0.00146 and p = 0.0137; hazard ratio - 1.12 and 1.11. The difference in median survival was as follows: 22 and 44 months for T4aN3aM0 (VII) ≈ T3N2M0 (VI) and the ligaments 28 and 23 months for T4bN3M0 (VII) ≈ T4N2M0 (VI), respectively. It is concluded that the movement of the subgroups of patients with gastric cancer TNM-from one system to another changed the risk of the event, the death of progression by 12 and 11%, respectively.

Table 1. Detected shift in survivability of the patients, stratified on the stages in accordance with the requirements of different TNM systems.

TNM stages, 6th edition	TNM stages, 7th edition	The range of differences in survival patients with gastric cancer , F test, Fisher's exact test	
		1st randomization group	2nd randomization group
I stage	I stage	Groups appeared minorities	
II stage	IIb stage	**p=0,14>0,05, n=21**	p=0,037<0,05, n=20
	IIa stage	**p=0,054>0,05, n=4**	**p=0,66>0,05, n=5**
IIIa stage	IIIa stage	p=0,019<0,05, n=14	p=0,0071<0,05, n=12
IIIa stage		p=0,002<0,05, n=14	p=0,0056<0,05, n=13
IIIa stage		p=0,00025<0,05, n=6	p=0,0001<0,05, n=12
IIIb stage	IIIb stage	p=0,0001<0,05, n=6	p=0,0001<0,05, n=27
IV stage	IIIc stage	p=0,0001<0,05, n=21	p=0,0001<0,05, n=18
	IIIc stage	p=0,01<0,05, n=21	p=0,0002<0,05, n=18
	IIIc stage	p=0,04<0,05, n=21	p=0,0003<0,05, n=11
	IIIc stage	p=0,0001<0,05, n=10	p=0,0001<0,05, n=10

Various survival of the same subgroup (TNM staging according to different systems) due to the fact that the number of patients in the same subgroup TNM has been varied, i.e. there is a shift or migrate patients from one subgroup to another. It was expected that no any differences between those groups, since it is the same patients. However, different systems of staging offer statistically significant difference in survival. 16 evaluations only three cases marked comparable value of patient survival: T3N1M0 (6th) and T4aN2M0 (7th), T4N1M0 (6th) and T4bN2M0 (7th), and T4N2M0 (6th) and T4bN3M0 (7th) ($p > 0,05$).

Table 2. Differences in the survival of radical operated patients with gastric cancer, stratified by groups of TNM.

TNM stages, 6th edition	**TNM stages, 7th edition**	The range of differences in survival patients with gastric cancer , F test, Fisher's exact test	
		1st randomization group	2nd randomization group
T2aN1Mo	T2N1Mo T2N2Mo	Groups appeared minorities	
T2bN1Mo	T3N1Mo T3N2Mo	Groups appeared minorities	
T3N1Mo	T4aN1Mo (n=20)	p=0,023<0,05	p=0,00029<0,05
	T4aN2Mo (n=25)	p=0,00239<0,05	**p=0,072>0,05**
T4N1Mo	T4bN1Mo (n=22)	p=0,00468<0,05	p=0,00326<0,05
	T4bN2Mo (n=12)	p=0,0164<0,05	**p=0,0526>0,05**
T2aN2Mo	T2N3Mo	Groups appeared minorities	
T2bN2Mo T2bN3Mo	T3N3Mo	Groups appeared minorities	
T3N2Mo	T4aN3Mo (n=14)	p=0,0147 <0,05	p=0,00018<0,05
T3N3Mo		p=0,0002<0,05	p=0,0002<0,05
T4N2Mo	T4bN3Mo (n=24)	**p=0,063>0,05**	p=0,0137<0,05
T4N3Mo		p=0,00056<0,05	p=0,0001<0,05

Over the past 10 years the oncological and surgical hospitals experienced a transition from 4th to the 5th, then the 6th and the coming 7th edition of the International Classification TNM. Could this fact affect the statistics and indicators of the quality of treatment of patients with gastric cancer? After all, the process took only 10-12 years. Numerous studies in medical literature were established on different classifying systems with different variables, e.g. the study of patients with gastric cancer on a fourth stage will now correctly be compared now with the 4th only, but also with 3a, 3b, 3c, and even a 2b-th stage.

We offer to the attention some differences between the 7th and 6^{th} edition of classification TNM. The 4th and 5th system of classification are not given here, so as not to clutter up the work.

1. Partition index T1 to T1a and T1b stages.

2. Subdivision T4 phenotype onto T4a and T4b stages.

3. T2a and T2b indexes are now missing, however 2a and 2b stages administered.

4. The numerical values of T and N indices gained new qualitative values, which will be discussed below.

5. The N3 index is now divided onto N3a & N3b.

6. Revision undergone stage 3 and 4: 4th stage now means only the presence of distant metastases; stage #3 is divided onto three stages: 3a, 3b, 3c.

7. Those TNM-combinations previously meant one stage now refer brand new stages:

^{6th}T1 N1 Mo = ^{7th}T1a,b N2 Mo

^{6th}T2a N1 Mo = ^{7th}T2 N2 Mo

^{6th}T2b N1 Mo = ^{7th}T3 N2 Mo, ^{7th}T3N1Mo

^{6th}T3 N1 Mo = ^{7th}T4a N1 Mo, ^{7th}T4a N2 Mo

^{6th}T4 N1 Mo = ^{7th}T4b N2 Mo

^{6th}T1 N2 Mo = ^{7th}T1a,b N3a Mo

^{6th}T2a N2 Mo = ^{7th}T2 N3a Mo

^{6th}T2b N2 Mo = ^{7th}T3 N3a Mo

^{6th}T3 N2 Mo = ^{7th}T4a N3a Mo

^{6th}T4 N2 Mo = ^{7th}T4b N3a Mo

^{6th}T2b N3 Mo = ^{7th}T3 N3b Mo

^{6th}T3 N3 Mo = ^{7th}T4a N3b Mo

Without changes or, more correct to say, almost without changes, remained:

^{6th}Tis No Mo = ^{7th}Tis No Mo

^{6th}T1 No Mo = ^{7th}T1a,b No Mo

^{6th}T1 N1 Mo = ^{7th}T1a,b N1 Mo

^{6th}T1 N3 Mo = ^{7th}T1a,b N3b Mo

^{6th}T2a N1 Mo = ^{7th}T2 N1 Mo

^{6th}T2a N3 Mo = ^{7th}T2 N3b Mo

^{6th}T4 N1 Mo = ^{7th}T4b N1 Mo

^{6th}T4 N3 Mo = ^{7th}T4b N3b Mo

Kim S. S. et al. [8] from the University College in Seoul, conducted a retrospective analysis of 266 patients with gastric cancer who were operated in 2000-2009, found no difference in survival of patients classified to 7th edition of the International Classification: between stages IIA and IIB, IIB and IIIA, and IIIA and IIIB (70% vs. 71%, p = 0.530; 71% vs. 80%, p = 0.703; 80% vs. 75%, p = 0.576, respectively), although the respective statistical difference in 5-year cumulative survival rates were found among classify to VI edition. Using T phase 7th version, 5-year survival rates did not differ between T2 and T3 (86% vs. 82%, p = 0.655). step using N, 5-year survival rates did not differ between N1 and N2, N3a and N3b (79% vs. 81%, p = 0.506; 41% vs. 17%, p = 0.895, respectively). Conclusions on that classification 7th is relatively worse prognostic possibilities in terms of determining the prognosis of gastric cancer compared with 6th edition.

Daniele Marrelli and colleagues. [9] analyzed 2090 patients with non-cardiac gastric cancer who were operated in the period 1991-2005. For comparison purposes, simulated evaluation of these patients by 7th TNM. Traces the changes in the distribution of patients with gastric cancer in stages in the 6th and 7th TNM version. Largely due to the shift of a large number of cases of the IB in stage IIA and of the IIIA and stage IV in stage IIIB, and IIIC. Cancer-sensitive 10-year survival was 53% ± 1%. Traces the significant differences in T (T2 vs. T3, P <0.001) and N categories (N1 vs. N2, P <0.001). Survival rates N3a subgroup (7-15 affected lymph nodes) was significantly better than N3b (> 15 lymph nodes; p <0.001). Stage IB and IIA 7th TNM showed a similar forecast, while among the other subgroups revealed significant differences. Analysis TNM categories within TNM stages VII showed heterogeneity in survival rates stages IIB, IIIB and IV. It is concluded that the seventh classification of AJCC / UICC TNM noncardia for gastric cancer shows the subgroup of patients with uneven outlook. Distribution by stages and phases-dependent survival has changed significantly compared to the 6th edition.

Is it possible, using probability theory, including statistical analysis of the probability of the procedure Cox, predict how often the phenomenon of "skipping" gastric cancer regional metastases escapes the observer, that is, surgeon, pathologist, chemotherapist? Since during surgery for gastric cancer, this phenomenon is not always detected (outermost collectors cannot be excised in all cases). Opportunity is to monitor early loco-regional recurrence. migration of patients from stage to stage at different lymphadenectomy procedures (D1, D2, D3) and the mathematical prediction of "failures" in the survival of patients at different ways of classifying (was used by the 6th and the 7th edition of TNM). The presence of "failure" in survival would indicate the presence of residual (left) collectors, even in the absence of loco-regional recurrence - an evidence of the phenomenon of Will Rogers . The study included patients with no evidence of distant metastases.

Objectives

The objectives of this work were to compare the influence of different types of classification onto patients' survival rate.

Materials and methods

The study, made on the abdominal oncosurgical department of Odessa Regional Oncology Center, included 188 patients operated for gastric cancer in the period 2007-2011. The study included only radically treated patients. The average age was 60,6 ± 10,5 years, gender content: men - 120, women - 68.

Table 3. Distribution of patients with gastric cancer by the age groups.

№	Age	Patients number
1.	30-39	7
2.	40-49	21
3.	50-59	54
4.	60-69	63
5.	70-79	35
6.	80-90	5

Total performed 126 total resection and 62 subtotal gastrectomy. Gastrectomy performed by the method of G.V. Bondar means forming a loop terminolateral coupling-like retrocolic esophago-jejunum anastomose interintestinal with entero-enteroanastomosis by Brown`s method. Distal subtotal resection in most cases finished with the formation retrocolic gastroenteroanastomosis Billroth-2 in Hofmeister-Finsterer modification.

We studied the life expectancy of patients with gastric cancer included in the study. Information about life expectancy has been obtained from the Regional Cancer Registry, updating data is 1 time in 3 months. Further, life tables were constructed for each of the group stage and the treatment method used. Survival was studied by constructing models of proportional hazards regression risks accorging to D.R.Cox (1972) by the formula:

$$hi\ (t) = ho\ (t) \times eb1X1 + b2X2 + b3X3 + ... + bnXr \text{ where}$$

h0 (t) – primary risk

b1 ... bn-regression coefficients

X1 ... XR-prognostic factors

When b = 0, hazard ratio is 1.

The observations were censored: For those patients with gastric cancer, with whom managed to keep in touch, censor = 0, if the patient dies, the censor was = 1. In survival analysis examined the frequency of events in time - the median survival of patients, i.e., time during which the population of patients with gastric cancer is cut in half. The starting point was the date of the operation, the scale of time - months of life of patients, the event - the death of the patient.

Regional Cancer Registry is an example of so-called censored sample. This term ‘censored’ means a sample should be analyzed mathematically, but which, because of objective and subjective reasons, does not contain complete information. Kaplan-Meier method, as a method of constructing life tables and other methods of dealing with censored samples. He has only one drawback: it does not allow to assess the significance of differences between the two survival curves.

The standard account of the right censoring - disposal of the patient to follow-up or death from other causes; and left clipping - uneven inclusion of patients in the study (patients included in the study in 2007, 2008, 2009, etc. years). By plotting scale Y - included the percentage of survivors S, and the scale of X - months of observation. The advantage of the Cox model is the possibility of adding a covariate, no need to properly stratify the group to justify the correctness of stratification in the log-rank (Logistic regression) and Kaplan-Mayer mathematical models.

The terms "survival analysis" and "cumulative survival" there are generally only for the proportionate Roxby James Cox regression. However, even in very serious jobs sometimes we still find the phrase "cumulative survival by Kaplan-Meier”.

Indeed, to the Student's t test dimensions compared samples should be greater than 30 observations, using Pearson's chi-squared test $\chi 2$ chi-square - not less than 20; using Fisher's exact test samples F size has virtually no value. For parametric samples necessary to study the law of distribution of feature-group sample to prove the existence of interdependence (relationships) between them and approve of the Gaussian distribution uniformity characteristic of the group. One of the most famous of tests for normality sign is the Kolmogorov-Smirnov test. One way to bring the sample to the normality is its logarithm, as we shall see below.

Wilcoxon T can be used if sample size of 5 to 50 study participants, while the number of groups should be the same. This figure is 50 - is the limit table value, in the case of the use of electronic calculations the upper limit is not limited. Criteria Fisher F and Student's t test designed for parametric two related samples with normal distibution feature. Wilcoxon T - 2 nonparametric related, for the same sample size (s). Pearson's chi-squared test and the nonparametric $\chi 2$. For more than 2 (3 or more group-selection) unrelated nonparametric samples with different number of members of the criterion Wilcoxon U-Mann-Whitney statistics and ANOVA (ANalysis Of Variance). U criterion may be used if the number of members of sample-20 - 60, but may be at a lower volume group.

Pearson criterion $\chi 2$ agreement has a maximum capacity of relative "(very) near" competing hypotheses [5]. These competing hypotheses in the case of our study were similar survival curves of patients with the same stage, which was removed a different number of lymph nodes.

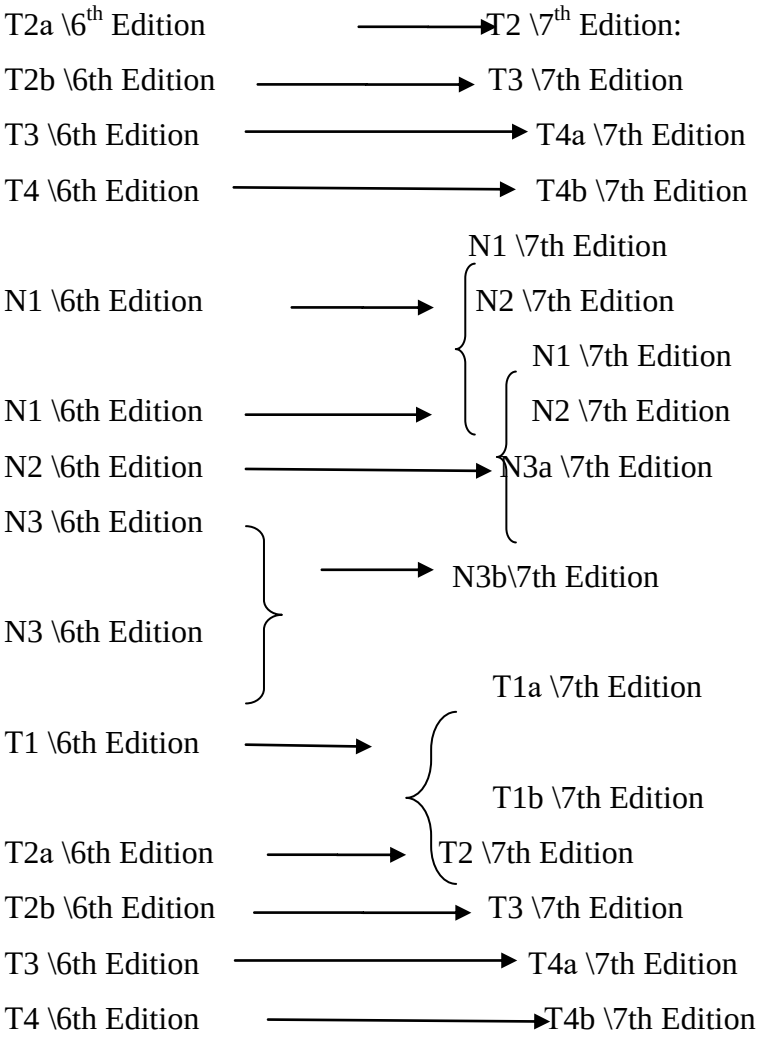
Despite this abundance of different criteria for assessing the validity of the relationship and the differences between the samples, the majority of interested researchers will always choose only between Fisher criterion F and Pearson $\chi 2$.

Correlation analysis is carried out using the criteria of the Pearson correlation r (r-Pearson) or Spearman r (r-Spearman's). The coefficient ranges from -1 to +1. For medical and biological researches is considered a high correlation number - 0.6 or 0.6. The negative correlation is also can be valuable. The value of 0.9 corresponds to almost absolute correlation between samples. The criterion of Pearson correlation of r and Spearman rank correlation criterion r are calculated for groups with a number of members of 5 or more.

Another essential to the calculation of indices in such studies is the odds ratio (OR). This unique index allows to estimate the probability of both favorable and unfavorable outcome. Thus researcher can predict the development of a particular outcome in a clinical trial. For example, if OR = 1 or close to 1, the odds of the event in the samples are the same. Axiom: the difference between the samples of groups is uncertain if the confidence interval includes 1. Thus, this is another criterion for the evaluation of the accuracy of the differences between the groups. In the following result we are often faced with a situation where p was less than 0.05, but the confidence interval did not include a digital value 1, which prompted at least not jump to negative conclusions.

As we have seen from the previous explanation, there is a so-called migration, a transition part of the patients from one stage to another TNM. The existence of such a transition has so far been confirmed only

speculative conclusion that what had previously been one step in the following classification will be different. Once again, let me remind yourself some of these examples.



Results

Attention is drawn to the fact how little in the medical literature drawn attention to the possibility of the presence of such a transition. After all, what used to be a stage, after quite simple and clear manipulation becomes another step T, N, M, etc. Survival rates of patients has been changed, occur changings in the ratio of men / women in groups, changing in the average age of the patients in groups, changing in the type of treatment, the patients who were subjected to finally such important descriptive elements, as an average, mode, standard deviation, etc. have been changed.

Table 4. Groups, where changing of classification system yielded statistically significant differences between the patients survival.

TNM stages, 6th edition	**TNM stages, 7th edition**	The range of differences in survival patients with gastric cancer , F test, Fisher's exact test	
		1st randomization group	2nd randomization group
T3N1Mo	T4aN1Mo (n=20)	p=0,023<0,05	p=0,00029<0,05
	T4aN2Mo (n=25)	p=0,00239<0,05	**p=0,072>0,05**
T4N1Mo	T4bN1Mo (n=22)	p=0,00468<0,05	p=0,00326<0,05
	T4bN2Mo (n=12)	p=0,0164<0,05	**p=0,0526>0,05**
T4N2Mo	T4bN3Mo (n=24)	**p=0,063>0,05**	p=0,0137<0,05
T4N3Mo		p=0,00056<0,05	p=0,0001<0,05

Thus, group T3N1Mo 6th reclassification compared with 2 relevant 7th:

T3N1Mo	T4aN1Mo (n=20)
	T4aN2Mo (n=25)

T4aN1Mo 7th (n=20) p=0,023<0,05 p=0,00029<0,05

T4aN2Mo 7th (n=25) p=0,00239<0,05 p=0,072>0,05.

As can be seen, regardless of randomization, when transfer from one classification to another occurs, patients had already different survival rate. This means that the so-called "State change" was everywhere, except in one case: p = 0.072> 0.05. Suchwise phenomenon occurred where T4N1Mo 6th passed comparison with 2 groups of the 7th:

T4N1Mo	T4bN1Mo (n=22)
	T4bN2Mo (n=12)

T4bN1Mo 7th (n=22) p=0,00468<0,05 p=0,00326<0,05

T4bN2Mo 7th (n=12) p=0,0164<0,05 p=0,0526>0,05

The same was the case in the other group with 34 patients, where as a result of migration from stage to stage the patient's lifespan changed. Only one of the three calculating comparison showed the absence of change: p = 0.0526> 0.05.

Other groups were relatively small in number for such comparisons, except as shown in the table below.

T3N2Mo	T4aN3Mo (n=14)
T3N3Mo	
T4N2Mo	T4bN3Mo (n=24)
T4N3Mo	

Both T3N2Mo7th and T3N3Mo7th inhere, according to all innovations, now match the another description by the seventh edition: T4aN3Mo.

Recall that the Fisher's exact test F and $\chi 2$ Pearson's chi-squared test can be used to compare the groups with only 2 arms. In this numerical (digital) value in such a table by using chi-square test cannot be less than 5. In the table numerical values were as follows:

T4aN1Mo (n=20)
T4aN2Mo (n=25)
T4bN1Mo (n=22)
T4bN2Mo (n=12)
T4aN3Mo (n=14)
T4bN3Mo (n=24)

Comparison was performed with a group of 6th revision, which had a similar number of groups of digital values.

Here phenomenon Will Rodger`s has found regardless of randomization group: p = 0.0147; p = 0.00018; p = 0.0002; p = 0.0002. Two groups randomization provide higher accuracy of calculations.

T3N2Mo 6th T4aN3Mo 7th (n=14) p=0,0147 <0,05 p=0,00018<0,05

T3N3Mo 6th p=0,0002<0,05 p=0,0002<0,05

Six T4N2Mo T4N3Mo and match the description to only two sevens, united under one heading - and it T4bN3 (a, b) Mo (N3 = metastasis There are 7 or more regional lymph nodes, T4b = tumor involves surrounding structures - OS). Recall:

N2 \6th Edition: 7-15 mts ⟶ N3a \7th Edition: 7-15 mts

N3\6th Edition >16mts

N3\6th Edition >16mts ⟶ N3b\7th Edition: >16 mts

T4 \6th Edition ⟶ T4b \7th Edition

T4N2Mo 6th T4bN3Mo 7th (n=24) p=0,063>0,05 p=0,0137<0,05

T4N3Mo 6th p=0,00056<0,05 p=0,0001<0,05

In the randomized group 1 in the case of the transfer of patients from T4N2Mo 6th in T4bN3 (a, b) Mo 7th, p = 0.063. With more than 0.05 - "state change" did not happen. Only in this case the introduction of the 7th classification did not affect the survival of patients with gastric cancer. In other cases, the desired phenomenon was observed and verified. The number of groups of patients was sufficient to assess the possibility of such test.

Another way to check the authenticity of our yet purely speculative conclusions on moving patients from one classification to another was an attempt to compare their survival depends on the stage. To do this, made a similar comparison of mathematical description of stages, as set out in the classifications.

Namely.

0stage TisNoMo **6th** = 0stage TisNoMo**7th**

1a stage T1NoMo **6th** = 1a stage T1a,bNoMo **7th**

1b stage T1N1Mo **6th** = 1b stage T1a,bN1Mo **7th**

1b stage T1N1Mo**6th** =2a stageT1a,bN2Mo**7th**

2 stage T2aN1Mo **6th** → 2a stage T2N1Mo **7th**; 2b stage T2N2Mo **7th**

2 stage T2bN1Mo **6th** → 2b stage T3N1Mo **7th**; 2b stage T3N2Mo **7th**

3a stage T3N1Mo **6th** → 3a stage T4aN1Mo **7th**; 3b stage T4aN2Mo **7th**

4 stage T4N1Mo \ **6th** → 3b stage T4bN1Mo **7th**; 3c stage T4bN2Mo **7th**

2stage T1N2Mo **6th**. =2bstageT1a,bN3aMo**7th**

3a stage T2aN2Mo **6th**. = 3a stage T2N3aMo **7th**

3a stage T2bN2Mo **6th**. = 3b stage T3N3aMo **7th**

3b stage T3N2Mo **6th**. = 3c stage T4aN3aMo **7th**

4 stage T4N2Mo **6th**. = 3c stage T4bN3aMo **7th**

4 stage T1N3Mo**6th**. = 2б stage T1a,bN3bMo**7th**

4 stage T2aN3Mo **6th**. = 3a stage T2N3bMo **7th**

4 stage T2bN3Mo **6th**. = 3б stage T3N3bMo **7th**

4 stage T3N3Mo **6th**. = 3c stage T4aN3bMo **7th**

4 stage T4N3Mo **6th**. = 3c stage T4bN3bMo **7th**

Table generalized comparison of survival in patients with gastric cancer graphs 6th revision groups of 7th review, which also has been randomized. Graphics themselves are not shown in the text to simplify the perception of the entire array of information.

Table 5. Group, where another method of staging yielded statistically significant differences between patients with gastric cancer survival stratified by stage.

TNM stages, 6th edition	TNM stages, 7th edition	The range of differences in survival patients with gastric cancer , F test, Fisher's exact test	
		1st randomization group	2nd randomization group
I stage	I stage	Groups appeared minorities	
II stage	IIb stage	**p=0,14>0,05, n=21**	p=0,037<0,05, n=20
	IIa stage	**p=0,054>0,05, n=4**	**p=0,66>0,05, n=5**

In this case, the situation with the number of patients in the subgroups was much more prosperous. Only the first stage is not pleased with the opportunity to test the theoretical conclusions.

II stage	IIb stage
	IIa stage

II stage IIb stage p=0,14>0,05, n=21 p=0,037<0,05, n=20

IIa stage p=0,054>0,05, n=4 p=0,66>0,05, n=5

Compares II and IIb stages in terms of changing survival for the mathematical verification of transfer patients reality from one group to another.

II stage IIb stage 21-20=1

IIa stage 4-5=-1

Only in one case, such a verification has been achieved: p = 0,037 <0,05, n = 20, when comparing the first randomized groups belonging to 7 from reclassification. In three other cases, the existence of the phenomenon of transition was rejected, but the number of patients there was unsatisfactorily low. Recall that it was considered statistically significant p <0.05, enough for biomedical research. Surprisingly, all this supreme statistical calculations completely coincided with the simplicity of arithmetic: 1 + 1 = 0.

IIIa stage	IIIa stage
IIIa stage	
IIIa stage	

IIIa stage IIIa stage p=0,019<0,05, n=14 p=0,0071<0,05, n=12

IIIa stage p=0,002<0,05, n=14 p=0,0056<0,05, n=13

IIIa stage p=0,00025<0,05, n=6 p=0,0001<0,05, n=12

The outcome of patients in stage IIIa 7th classification system in exactly the same stage IIIa previous classifications in all cases was confirmed.

IIIa stage 14-12=2

IIIa stage 14-13=1

IIIa stage 6-12=-6

Will Rodger`s phenomenon here confirmed. Statistical indicators, including the most important from the point of view of the oncologist - a change of survival – has been radically changed. In some cases, the

accuracy was p <0.001, and in one case even <0.0001. The total number of patients n = 71, provided that the use of Fisher's exact test is sufficient to confirm the statistical differences, even though the number of groups from 6 to 14. The migration of 2 + 1 + -6 = -3.

IIIb stage	IIIb stage

The same data was odtained when compared IIIb of 6th stage and IIIb of 7th editions. The resulting mathematical parameters are: p = 0.0001 <0.05, n = 6 and p = 0.0001 <0.05, n = 27.

IV stage	IIIc stage
	IIIc stage
	IIIc stage
	IIIc stage

IV stage	IIIc stage	p=0,0001<0,05, n=21	p=0,0001<0,05, n=18
	IIIc stage	p=0,01<0,05, n=21	p=0,0002<0,05, n=18
	IIIc stage	p=0,04<0,05, n=21	p=0,0003<0,05, n=11
	IIIc stage	p=0,0001<0,05, n=10	p=0,0001<0,05, n=10

The same data obtained for the transition from IV to IIIc stage. n = 130. Reformatting the group in the 7th revision led to a radical change in the statistics. p = 0.0001; p = 0.0001; p = 0.01; p = 0.0002; p = 0.04; p = 0.0003; p = 0.0001; p = 0.0001. Number of transferred patients: 16.

IV stage	IIIc stage	21-18=3
	IIIc stage	21-18=3
	IIIc stage	21-11=10
	IIIc stage	10-10=0.

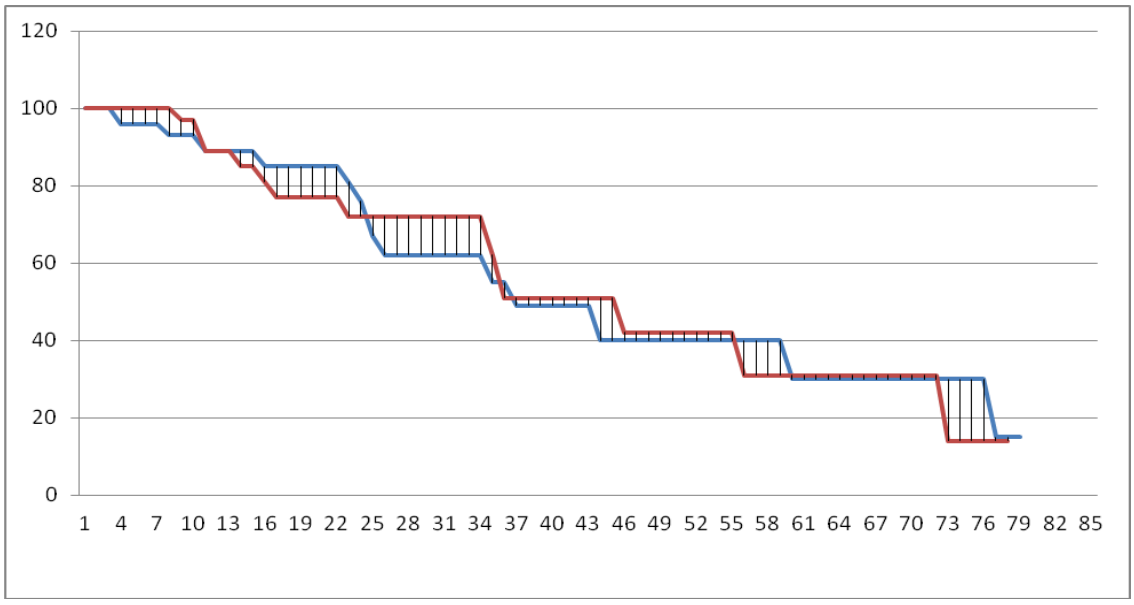
Another interesting event was the comparison group in the same revision (what medical researchers usually did). The classification mission is to provide differences in the survival rates between the groups. So first, the 6th revision. As far as it is able to divide into groups of patients with gastric cancer was significantly different survival. Going forward, we must say that the second classification of patients in our sample proved to be qualitatively better level.

Table 6. Reliability of differences between those survival curves, created by 6th Classification.

Differences in survival of subgroups according 6th revision of the UICC		
There is differences in survival		**There is no differences in survival**
p<0,05	p<0,01	p>0,05
T2No → T2N1 p= 0,033	T2No → T2N2, p= 0,0088	T2N2 → T2N1, p= 0,62
T2N2 → T3N2 p= 0,01	T2No → T3N1, p= 0,00029	T2No → T3No, p= 0,1
T3N2 → T3No p= 0,039	T3N1 → T2N1, p= 0,00016	T3No → T2N1, p= 0,66
T3N3 → T4No p= 0,0148	T2N2 → T3N1, p= 0,0005	T3No → T2N2, p= 0,85
T2No → T4N1 p= 0,041	T3No → T3N1, p= 0,0002	T4No → T2N1, p= 0,27
T4N2 → T2No p= 0,028	T2No → T3N2, p= 0,0001	T2N2 → T4No, p= 0,55
T3N2 → T4N2 p= 0,035	T3N2 → T3N1, p= 0,0002	T4No → T3No, p= 0,13
T4N3 → T4N1 p= 0,0199	T2No → T3N3, p= 0,0003	T3N3 → T3N2, p= 0,46
T4N3 → T2N2 p= 0,0125	T3N3 → T2N1, p= 0,0006	T4No → T3N2, p= 0,12
T4N3 → T2N1 p= 0,024	T3N3 → T2N2, p= 0,0002	T4N1 → T4No, p= 0,24
	T3N3 → T3No, p= 0,00015	T3No → T4N1, p= 0,72
	T3N3 → T3N1, p= 0,0001	T2N2 → T4N1, p= 0,86
	T4No → T2No, p= 0,0013	T4N1 → T2N1, p= 0,94
	T4No → T3N1, p= 0,0001	T4N2 → T2N1, p= 0,76
	T3N3 → T4N1, p= 0,00044	T4N2 → T2N2, p= 0,59
	T3N2 → T4N1, p= 0,0092	T4N2 → T3No, p= 0,49
	T4N1 → T3N1, p= 0,0001	T4N2 → T4No, p= 0,48
	T4No → T2No, p= 0,0013	T4N1 → T4N2, p= 0,5
	T2N2 → T3N2, p= 0,0057	T4N3 → T4No, p= 0,35
	T4N2 → T3N1, p= 0,0001	T4N3 → T3N3, p= 0,23
	T4N2 → T3N3, p= 0,0032	T4N3 → T3N2, p= 0,68
	T4No → T2No, p= 0,0013	
	T4N3 → T3N1, p= 0,0001	
	T4N3 → T3No, p= 0,0086	
	T4N3 → T2No, p= 0,0002	

Thus, a high mathematical precision was able to show that most of the groups of patients created the 6th revision of the classification TNM, statistically different. From our point of view, this is the goal of creating a classification: the creation of a classification system that with its help you can create groups, differing from each other by objective evidence. In this case we observe and analyze the differences in survival between groups. 21 pairs of survival curves were not differences compared 25 pairs of survival curves of RG - ultra-high power differences $p < 0.01$, and in many cases, $p < 0.001$ and $p < 0.0001$. 10 pairs of survival curves were statistically significant differences between them with the power of $p < 0.05$. Charts are not given, so as not to clutter up the story.

"Step" survival curves between them and the presence of "crossroads" in the calculation did not matter. Calculation was based on D.R.Cox, not by the log-rank and Kaplan-Meier for which such "descriptive" characteristics are important. For Cox proportional hazards model visualization graphs critical value almost does not matter. Survival curves in real life, may intersect with each other several times. Example.



P=0,6584

Table 7. Stages calculate survival rate for 3A stage according to different TNM systems.

Control group			Main group		
Table of survival	Month	% of survived	Table of survival	Month	% of survived
6,24,1	5.0000	0.9644	1,10,1	10.0000	0.9645
12,38,1	9.0000	0.9273	10,37,1	12.0000	0.8937
14,61,1	12.0000	0.8887	11,37,1	15.0000	0.8531
9,26,1	17.0000	0.8484	14,74,1	17.0000	0.8105
7,25,1	24.0000	0.8060	2,12,1	18.0000	0.7655
9,27,1	25.0000	0.7613	7,24,1	24.0000	0.7177
8,26,1	26.0000	0.7613	5,17,1	36.0000	0.6220
5,17,1	27.0000	0.6159	6,18,1	37.0000	0.5084
2,9,1	36.0000	0.5543	4,15,1	47.0000	0.4224
3,12,1	38.0000	0.4849	3,12,1	57.0000	0.3132
15,78,1	45.0000	0.4039	8,36,1	74.0000	0.1409
11,36,1	61.0000	0.3023	9,36,1		
13,45,1	78.0000	0.1484	13,57,1		
1,5,1			12,47,1		
10,24,0			13,10,0		
4,38,0			4,37,0		
2,61,0			3,37,0		
7,26,0			10,74,0		
9,25,0			12,12,0		
7,27,0			7,24,0		
8,26,0			9,17,0		
11,17,0			8,18,0		
14,9,0			10,15,0		
13,12,0			11,12,0		
1,78,0			6,36,0		
5,36,0			5,36,0		
3,45,0			1,57,0		
15,5,0			2,47,0		
Coefficients, Std Errs, Signif, and Conf Intervs...			Coefficients, Std Errs, Signif, and Conf Intervs...		
Var Coeff. StdErr p Lo95% Hi95%			Var Coeff. StdErr p Lo95% Hi95%		
1 0.0089 0.0546 0.8701 -0.0975 0.1153			1 -0.0381 0.0652 0.5590 -0.1653 0.0891		

The next step was to conduct a similar analysis for the 7th TNM classification. What if this same group of patients with gastric cancer, be classified not by the 6th, but now by the 7th revision of the classification. Then to compare how will differ obtained TN-group (Index M is always "0" in this case, since it was only patients with local disease).

To achieve greater purity of this experiment, the patients were stratified randomly into two groups, in which comparisons were made. Here's present what happened.

Table 8. The interaction between stages and the significance of differences in the survival of subgroups TNM classification of gastric cancer patients 7th revision of the UICC

	1st group	2nd group
1	T4aNo → T4aN1 p= 0,23>0,05	T4aNo → T4aN1 p= 0,88>0,05
2	T4aNo → T4bNo p= 0,42>0,05	T4aNo → T4bNo p= 0,75>0,05
3	T4aN1 → T4bNo p= 0,71>0,05	T4aN1 → T4bNo p= 0,87>0,05
4	T4bNo → T4bN1 p= 0,56>0,05	T4bNo → T4bN1 p= 0,72>0,05
5	T4bN1 → T4aN1 p= 0,84>0,05	T4bN1 → T4aN1 p= 0,60>0,05
6	T4bN1 → T4aNo p= 0,31>0,05	T4bN1 → T4aNo p= 0,42>0,05
7	T4aNo → T4aN2 = 0,12>0,05	T4aN2 → T4bN1 p= 0,61>0,05
8	T4aN2 → T4aN1 p= 0,47>0,05	T4aN2 → T4bNo p= 0,36>0,05
9	T4aN2 → T4bNo p= 0,28>0,05	T4aN2 → T4aN1 p= 0,29>0,05
10	T4bN1 → T4aN2 p= 0,64>0,05	T4aN2 → T4aNo p= 0,13>0,05
11	T4bN2 → T4aN2 p= 0,46>0,05	T4bN2 → T4aN2 p= 0,45>0,05
12	T4bN2 → T4bN1 p= 0,74>0,05	T4bN2 → T4bN1 p= 0,19>0,05
13	T4bN2 → T4bNo p= 0,89>0,05	T4bN2 → T4bNo p= 0,99>0,05
14	T4bN2 → T4aN1 p= 0,87>0,05	T4bN2 → T4aN1 p= 0,91>0,05
15	T4bN2 → T4aNo p= 0,61>0,05	T4bN2 → T4aNo p= 0,66>0,05
16	T4aN3 → T4bN2 p= 0,20>0,05	T4aN3 → T4bN2 p= 0,44>0,05
17	T4aN3 → T4aN2 p= 0,21>0,05	T4aN3 → T4aN2 p= 0,87>0,05
18	T4aN3 → T4bN1 p= 0,41>0,05	T4aN3 → T4bN1 p= 0,051>0,05
19	T4aN3 → T4bNo p= 0,73>0,05	T4aN3 → T4bNo p= 0,39>0,05
20	T4aN3 → T4aN1 p= 0,51>0,05	T4aN3 → T4aN1 p= 0,33>0,05
21	T4aN3 → T4aNo p= 0,96>0,05	T4aN3 → T4aNo p= 0,21>0,05
22	T4bN3 → T4aNo p= 0,41>0,05	T4bN3 → T4aNo p= 0,64>0,05
23	T4bN3 → T4aN1 p= 0,89>0,05	T4bN3 → T4aN1 p= 0,89>0,05
24	T4bN3 → T4bNo p= 0,66>0,05	T4bN3 → T4bNo p= 0,66>0,05
25	T4bN3 → T4bN1 p= 0,96>0,05	T4bN3 → T4bN1 p= 0,54>0,05
26	T4bN3 → T4aN2 p= 0,65>0,05	T4bN3 → T4aN2 p= 0,29>0,05
27	T4bN3 → T4bN2 p= 0,59>0,05	T4bN3 → T4bN2 p= 0,93>0,05
28	T4bN3 → T4aN3 p= 0,49>0,05	T4bN3 → T4aN3 p= 0,34>0,05

As you remember, comparing survival rates classified by the 6th edition of the classification of patients managed to obtain three groups. Groups differed in the strength of significant differences in survival in patients with gastric cancer. Groups have 21, 25 and 10 sub-groups in which the survival curves were compared by p-criteria. Thus the power of manufactured classification can be appreciated be the particular criteria: its capacity to demonstrate the survival difference between those groups mathematically.

Unfortunately, this same group of patients classified now on the 7th TNM classification, the differences in survival rates between similar groups-family, we could not fix. This fact is reflected in Table 8. The probability of finding differences between the stratified 7th classification groups was always less than 95%. But this is not enough for biomedical research.

Present work has only a research interest and in any case not intended to criticism classifications. We hope that in the recruitment process obtain more material to trace brand new, more interesting trends. Although the number of our group was comparable with two of those four known studies: 188 ours against 295 Sumin Chae et al., 266 Kim SS et al., 609 Shiro Kikuchi et al., 2090 patients Daniele Marrelli and colleagues.

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