

LYMPH NODE DISSECTION IMPACT ON LONG-TERM SURVIVAL RATE OF GASTRIC CANCER PATIENTS IN UKRAINE

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ABSTRACT

Over a period of 2007-2011 188 stomach cancer (SC) patients have been included in the research in abdominal oncosurgical department of Odessa oncological center. Volume of lymph node dissections differed by quantity of lymph nodes to be removed. All patients were divided into three groups. Patients with D1 or D1+ lymph node dissections have been performed, totally 90 patients are included in group of historical control. In all cases so-called lymph node dissections for principal reasons have been executed. The multifactorial analysis of patients survival is implemented depending on a type of a lymph node dissections, a stage of the cancer, number of involved lymph nodes, involvement of the tumoral microcirculatory net (ly is carried out, v) signs of a perineural invasion (Nev), availability of residual tumoral tissue (R), degree of a differentiation (G). Regardless of a disease stage, SC at 60 % of patients, represented with initially hematologically disseminated disease. 40 % of SC's had no signs of intratumoral microcirculatory net involvement even in case of more than 15 regional lymph nodes are involved.

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Introduction. Removal of lymph nodes as collectors of regional metastasis leaves a standard procedure at various locations of malignancies. The concept of "dissection" includes removal of lymph nodes, lymph vessels, and fat, located near these structures. Regional lymph node dissection is a standard surgical maneuver in stomach cancer (SC). The consequence of lymph collectors dissection has elaborated in the fundamental provisions on SC (General Rules for Gastric Cancer Study) published by the Japanese research society for gastric cancer (Japanese Research Society for Gastric Cancer – JRSGC). For the first time, according to the literature single block removing of local cancer metastasis was performed at the beginning of the 60-ies of the 20 century by D.Jinnai.

At present, depending on the volume of dissection of lymphatic tissue in SC, there are three variants of gastrectomy [1]:

1. Standard gastrectomy, which runs D1 dissection, including paragastric lymph nodes: 1-6 of the Japanese classification of regional lymph nodes.

2. Radical gastrectomy, with D2 lymph node dissection, including lymph collectors located along the branches of the celiac artery: 7-11 lymph nodes.

3. Advanced radical gastrectomy, includes 12-16 retroperitoneal lymph nodes.

Retroperitoneal metastases in the lymph nodes under the 6th Edition of UICC TNM belong to category M1. According to the international classification and the domestic guides [1] to the group of regional lymph nodes rank regional lymph nodes groups 1-12. Most of the lymph nodes of N3 category JRSGC in accordance with the classification of the International Cancer Union belongs to category M1, fourth stage of SC.

However, in view of the fact that the set of patients in the study is dated 2007-2011, we applied the domestic classification. If you take a principled position, in accordance with JRSGC, our group D3 lymph node dissections D2 + group you can name. Differences with the D2 arm remains totally clear and transparent: an additional 13-15 lymph nodes groups dissection.

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

Materials and methods. A study carried out on the basis of abdominal oncosurgery department of Odessa regional oncologic dispensary, 188 patients operated on for stomach cancer in the period 2007-2011 have analyzed retrospectively. The study was retrospective, single-center, non-randomized, includes only the radical or shareware radically operated patients. The average age was 60.6 ± 10.5 years, gender distribution: 120 men, 68 women. The detailed distribution of patients by age is presented in table 1.

Table 1. Distribution of Gastric Cancer Patients by Age Group

№	Age group	Number of patients
1.	30-39 years	7
2.	40-49 years	21
3.	50-59 years	54
4.	60-69 years	63
5.	70-79 years	35
6.	80-90 years	5

126 total gastrectomy and 62 distal subtotal resection were included into the list. Total gastrectomies were performed according to Bondar method [2] with the formation of the anti-reflux terminal-lateral mufti-like retro-colic esophago-jejenum anastomosis loop with entero-anastomose according to Brown methodic. Distal subtotal resection was accomplished in the most cases by performing retro-colic gastroenteroanastomosis by Goffmeister-Finsterer according to Bilroth-2 modification.

Majority of these operations were accompanied by multiple organ resections. Colon, liver, pancreas, diaphragm, abdominal wall, left and right kidneys, right and left adrenal glands, small intestine, retroperitoneal space

Table 3. Number of Removed Lymph Nodes, Depending on the Type of Operation, the Number of Operations

Type of operation	Type of lymph node dissection	Average number of lymph nodes to be removed	Number of operations
1. Standard	D 1	$8,9 \pm 0,9$	90
2. Radical	D 2	$31,6 \pm 0,7$	65
3. Advanced gastrectomy	D 3	$37,9 \pm 0,9$	33

Each removed tissue have examined histologically. Distribution of distant lymph node

considered as an adjacent for stomach structures [3]. Intraparietal spread into esophageal wall is noted at 31 (16.49 %) the patient, requiring resection of the subdiaphragmatic and, in some cases, intradiaphragmatic esophageal segments. In 3 cases, Osawa-Harlock operation with resection of distal esophageal segment was performed. In 28 cases – resection of the subdiaphragmatic segment by Savinykh. Intraparietal spread to the duodenum was found in 2 (1.06 %) patients and were being classified by the maximal depth of invasion evaluated morphologically. Resection of the pancreatic tail met the 74 patients (39.36 %) however true histological invasion into the pancreas found in 5 patients (2.66 %), atypical liver resection in 9 patients (4.79 %), anatomical resection-3 patients (1.59 %). Splenectomy was done in 153 cases (81.38 %), most frequent as a principal approach, as a component of D1 + lymph node dissection. In 5 cases there was metastatic spleen capsule affection (2.66 %). In 3 cases carried out dissection of the gate of the spleen as a part of spleen-saving operation (1.59 %).

The conclusions were made by p Wilcoxon less than 0.05, which is considered sufficient for biological and medical investigations. The correlation was considered to be high if the index R Pearson's 0.7 – 0.9, very high-more than 0.9, see (Table 2).

Table 2. Interpretation of the Pearson Product Moment Correlation Coefficient

Value	Interpretation
Up to 0,2	Very poor correlation
Up to 0,5	Poor correlation
Up to 0,7	Mild correlation
Up to 0,9	Strong correlation
Beyond 0,9	Very strong correlation

Lymph node dissections were classified by number of distant lymph nodes to be dissected. All the patients were divided into three groups. A group of historical control patients whom D1 or D1 + lymph node dissection were performed, 90 patients. The main group consisted of 33 patients whom D3 dissection was completed, the comparison group – 65 patients with D2 dissection. The results are presented in the table.

groups by JGCA classification began to do recently. Removed lymph nodes have been

ranked in 7 groups: paraogastric of large curvature (№ 4-6), paraogastric of small curvature (№ 1, 3, 5), lymph nodes along the branches of the splanchnic trunk (№ 7-11), renal and hepatic ligaments of the liver and duodenum (№ 12), retropancreatic (№13), the root of the mesentery of large intestine (№14-15), aortic lymph nodes (№ 16). Paraaortal dissection was performed to the level 16a2.

Still remains unclear the question should the resection of splenic artery during (and the distal hemipancreatosplicectomy as a matter of principle, oncological reason) with arcade Kirk as stage D2 lymph node dissection to be executed.

For staging used 6-th Edition of TNM classification, distribution of patients in stages is presented in Table 4.

Table 4. Distribution of Gastric Cancer Patients in Stages

Stage	TNM, 6-th edition	Number of patients			
		According to stage		According to pTNM	
		Absolute values	Percentage	Absolute values	Percentage
1A	pT1NoMo	1	0,53	1	0,53
1B	pT1N1Mo	14	7,45	0	0
	pT2aNoMo			14	7,45
	pT2bNoMo			0	0
2	pT1N2Mo	14	7,45	0	0
	pT2aN1Mo			1	0,53
	pT2bN1Mo			4	2,13
	pT3NoMo			9	4,78
3A	pT2aN2Mo	60	31,91	1	0,53
	pT2bN2Mo			4	2,13
	pT4NoMo			24	12,77
	pT3N1Mo			31	16,49
3B	pT3N2Mo	14	7,45	14	7,45
4	pT4N1Mo	85	45,21	25	13,29
	pT4N2Mo			32	17,02
	pT4N3Mo			15	7,98
	pT1N3Mo			0	0
	pT2aN3Mo			3	1,59
	pT2bN3Mo				
	pT3N3Mo			5	2,66
	pT _{любое} N _{любое} M1			5	2,66

Where rT1 – tumor of the stomach, infiltrates the basal membrane and the submucosal layer;

rT2a – tumor, infiltrates muscular layer;

rT2b – tumor, infiltrates subserous layer;

rT3 – tumor, infiltrates serosa layer (visceral peritoneum) invasion into nearby structures;

rT4 – tumor spreads to nearby structures.

In table 5 presents the characteristics of patients according to the degree of the local prevalence of SC.

Table 5. Characteristics of Patients According to the Degree of the Local Prevalence of SC

T - criteria	Number of patients in absolute values	Percentage
pT1	1	0,53
pT2a	17	9,04
pT2b	10	5,32
pT3	61	32,45
pT4	99	52,66

For the convenience of further calculations of survival and stratification of patients they were divided into groups with differentiated cancers, which include highly – and moderately differentiated tumors and patients with poorly differentiated tumor forms: it included low and undifferentiated gastric cancers. The number of patients with differentiated forms of cancers – 91 (48.40 %), with undifferentiated – 97 (51.59 %).

Patients with macroscopically-defined residual tumor tissue had not been included in the study R2, R1 residual tumor was found in 31 patients (16.5 %). In addition to determining the degree of differentiation of the primary tumor, tumor incidence in the stomach, invasion into surrounding structures, etc., was the number of the affected lymph node groups Nos. 1-16, presence of tumor emboli in capillary veins (v.), signs of perineural invasion (Nev), the presence of residual tumor tissue (R).

The degree of vascular (v, a venous and lymphatic, ly) involvement by JRS GC [4]:

v0, ly0-no vascular invasion;

v1, ly1-minimal vascular invasion;

v2, ly2-moderate vascular invasion;

v3 ly3 is expressed (heavy) vascular invasion. The reason for the lack of differentiation of venous and lymphatic invasion of 188 patients was the painting of micro prepartes by hematoxylin-eosin (H&E), while according to the literature [4] for the follow-up of differences is Victoria-blue staining or Elastica stainig, which we didn't have. Pathomorphological venous and lymphatic vessels tracked the type of muscular walls (venues with optical microscopy more muscle, lymphatic vessels have the appearance of fissure). Capillary vessels without a muscular component to distinguish, in most micropreparations only capillaries.

Differentiation of the tumor by microscopic infiltration INF (α -, β -, γ -type type) as well. On the degree of involvement of the microcirculatory net in the tumor process (invasion in micro venaes and lymph capillaries, the presence of tumor emboli – OE) patients were divided into Vo and V1. In the group of Vo patients included v0-1, ly0-1 tumors; Group V1 v2-3 patients, ly2-3 tumors. This is to avoid too many patient's groups with a small number of patients in each group. Table 6 shows the distribution of SC in stages depending on the presence of tumor emboli (OE).

Table 6. The distribution of patients in stages, depending on the availability of the MA in microvasal a tumor

Stage	Presence emboli in a vascular environment				Ratio of occurrence of a sign in a stage
	Vo		V1		
	Absolute values	Percentage	Absolute values	Percentage	
1A	1	0,53 %	0	0 %	0 %
1B	13	6,91 %	1	0,53 %	7,14 %
2	7	3,72 %	7	3,72 %	50 %
3A	43	22,87 %	17	9,04 %	28,33 %
3B	13	6,91 %	1	0,53 %	7,14 %
4	67	35,64 %	18	9,58 %	21,18 %
Sum	144	76,59 %	44	23,40 %	23,4 %

Results. Patients who underwent less than 15 lymph nodes removing during gastrectomy or subtotal gastrectomy was only in the historical controls. Unfortunately, in modern conditions is difficult to manufacture and study 30-40 frozen sections obtained from one operational preparation (D3 = 40 removed lymph nodes), which sought to combine the intra-operative cytological and histological study. We has been performed only one section of each removed lymph node (by JGCA research it is essential to do at least three slices of each remote lymph node).

Postoperative lethality was 4.3 %. The highest mortality was in Group D3 – 6.1 %. There has been a gradual decline in the fatality rate during the experience has been grown up in recent years, the death rate after gastrectomy was 2 %. In any case, among the 188 patients, mortality was not related to the leakage of esophago-jejunoanastomosis or duodenum. Immediate treatment results are presented in table 7.

Table 7. Postoperative lethality depending on the type of operation

Type of operation	Number of the dead, absolute values	Percentage
D1-lymph node dissection procedure	3	3,3 %
D2-lymph node dissection procedure	3	4,6 %
D3-lymph node dissection procedure	2	6,1 %

Patient`s survival rate was monitored using Odessa regional cancer registry. 2 patients were excluded from the list, 4 – have died from other causes.

The frequency of vascular involvement in the study was 23.4 %: 44 of 188 studied patients. The presence of OE in a vascular tumor microenvironment is not always correlates to the stage of the disease. A small number of patients with present histological examination found MA in stage 3B, perhaps due to the small sample size – 14 persons; as well as the presence of two neighboring groups – 3A and 4 stages patients with phenotype $T_4N_{any}Mo$. Such tumors are prone to hematogenic dissemination more than to local growth. 3A stage, which consisted of patients with $rT2aN2Mo$, $rT2bN2Mo$, $rT4NoMo$, $rT3N1Mo$ SC phenotypes, correlates by absolute number of V1 4 group stage patients (with more advanced $rT4N1Mo$, $rT4N2Mo$, $rT4N3Mo$, $rT1N3Mo$, $rT2aN3Mo$, $rT2bN3Mo$, $rT3N3Mo$, as well as tumors with macroscopically-defined hematogenic dissemination $T_{any}N_{any}M_1$). This difference in the pathohistological picture in the earlier stages witness a different biological properties of cancers than the impact correct staging (all macro-and microscope slides were explored and staged by the same pathologist). The same trend can be seen and in the study of the prevalence of perinevral growth at various stages of SC. The number of N + tumor in 3A and 4 stages is the same.

Index R is the numeric value of coefficient of Pearson linear correlation, p-reliability, SEE- the standard error of calculations. Absence of perineural growth in the study was the most sensitive factor with direct correlation, which is close to 1.0 in relation to the absence of perivascular growth with likelihood of radical resection, i.e. favorable predicting factors ($R = 0.98$, $SEE = 4.41$, $p = 0.0001$). Identified an inverse proportional dependence between Nev and the presence of perivascular growth as well as residual tumor tissue presence.

The presence of perineural growth does not correlate with any predicting factors, i.e., it was not a significant prognostic factor. The influence of lymph node dissection type has impact on a survival rate of patients depending on the stage of the SC. The degree of this influence was evaluated based on the presence/absence perineural tumor growth. D3 dissection increased the survival rate of patients with SC Nev\0 at 1B

and 3A stages, D2 dissection in Nev\0 gave an advantage in 2nd and 3rd stages. The advantage of lymph node dissection at Nev\0 in 4th stage were not statistically proved. In the perineural tumor growth present, that is Nev\1, D3 dissection has had a positive effect on the survival rate in 2nd and 3rd stages, and D2 dissection increased survival only in 3A, Nev\1 stage.

In 1a, Nev\1 and 3B, Nev\1 stages of SC examined groups were too small. The difference in life expectancy depending on perineural growth, regardless of the stage depth and lymph node dissection is as follows. Life expectancy at Nev\0 – 24.6 ± 6.0 months and for Nev\1 – 12.9 ± 6.0 months ($p = 0.0092$, $F = 882$). Thus, regardless of correlation with other factors, perineural growth believed to be the negative predicting factor. Table 8 shows the distribution of patients in stages, depending on the availability of R1.

Table 8. The distribution of patients in stages, depending on the availability of microscopically defined residual tumor tissue

Stage	Availability of microscopically defined residual tumor tissue				Ratio of occurrence of a sign in a stage
	Ro		R1		
	Absolute values	Percentage	Absolute values	Percentage	
1A	1	0,53 %	0	0 %	0 %
1B	14	2,13 %	0	0 %	0 %
2	13	7,98 %	1	0,53 %	7,14 %
3A	50	26,59 %	10	5,32 %	16,67 %
3B	12	6,38 %	2	1,06 %	14,29 %
4	67	35,64 %	18	9,57 %	21,18 %
Sum	157	83,51 %	31	16,49 %	

Conclusions.

1. 60 % of SC patients, irrespectively of the stage of the disease, had obviously haematogenously disseminated disease: $R = 0.42$ ($SEE = 1.59$, $p = 0.083$).

2. 40 % SC had no signs of microcirculatory net involvement even in the case of metastases present in more than 15 regional lymph nodes.

3. The absence of perineural cancerous infiltration was manifested as the most sensitive test, with a statistic power of correlation close to 1.0 to the lack of dissemination and likelihood of hematogenic radical resection, i.e. favorable way for SC follow up ($p = 0.0001$).

4. It is essential to find some novel predicting markers for further correct selecting patients for advanced lymph node dissections.

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