# Study of the advanced lymph node dissections impact on survival rate of gastric cancer patients

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**Summary.** Over a period of 2007-2011 188 stomach cancer (SC) patients have been included in the research in abdominal oncosurgical department of Odessa regional oncological dispensary. It was retrospective, one-center, nonrandomized research. Volume of lymph node dissections differed by quantity of lymph nodes to be removed. All patients were divided into three arms. Patients to whom D1 or D1+ lymph node dissections have been performed, totally 90 patients are included in group of historical control. The main group includes 33 patients to whom D3 lymph node dissections is executed and, finally, control group – 65 patients dissected up to the D2 volume. In all cases so-called lymph node dissections for principal reasons have been executed. The multiple-factor analysis of patients survival is implemented depending on a type of a lymph node dissections, a stage of the cancer, number of the involved lymph nodes, involvements of the tumoral microcirculatory net (ly is carried out, v) signs of a perinevral invasion (Nev), availability of residual tumoral tissue (R), degree of a differentiation (G). The cancer of a stomach at 60% of patients, regardless of a disease stage, represented with initially hematologicaly disseminated disease. 40% of SC`s had no signs of intratumoral microcirculatory net involvement even in the case of more than 15 regional lymph nodes are involved. In the absence of a SC perinevral invasion appeared to be the most precise predictive marker. The conclusion is made some brand new additional prognostic factors could play a crucial role in more accurate patients selection for expanded lymph node dissections [8,9,11].

**Key words:** cancer of the stomach, extended lymph node dissections.

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 nearby of those structures. Regional lymph node dissection is a standard surgical manoeuvre in cancer of the stomach (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 cancer of the stomach, there are three variants of gastrectomy [2]:

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

Retroperitoneal metastases in the lymph nodes under the 6th Edition of UICC TNM belongs to category M1. According to the international classification and the domestic guides [2] 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.

V.I. Chissov, A.H. Trachtenberg, A.I. Paches [2] refer to the category D2 lymph node dissection removing the 1 – 12 groups, D3-13 – 16 groups, including No. 16a1, 16a2, 16b1. D4-paraaortal lymph node – dissections from the lower level to the bifurcation of the aorta mesenteric artery – No. 16b2. This is the fundamental difference of approach to expanded lymph node dissections and JRSGC standards. At the same time, the analysis of the literature on the subject shows there is a slow but steady tendency to the escalation of removing lymph node groups quantity towards D3 and N3 category [1].

According to the standards JGCA, Gastric Cancer Association Japanese [5] provides 4 types of radical surgical resection of the stomach: modified gastrectomy, standard gastrectomy and extended or advanced gastrectomy. Respectively modified gastrectomy and D1 + lymph node dissection volume corresponds to the removal of 7 groups of lymph nodes, lymph nodes along the left gastric artery. Modified gastrectomy in accordance of this classification includes the removal of 7, 8A and 9 groups of lymphatic nodes. To clarify should we perform D2 or D3 dissection we detail the location of the tumor in the stomach. Table 1 shows the classification of radical surgical resections according to Japanese Research Society for Gastric Cancer.

Table 1. Types of radical surgical resection according to JRSGC.

| Type of operation | Type of operation | Type of lymph node dissection | Options |
|---|---|---|---|
| Endoscopic mucous resection | Mucousectomy | no | no |
| Modified gastrectomy, type A | Partial gastrectomy, Total resection | D1+ lymph nodes along the left gastric artery | Preservation of a vagal nerve, pylorus-sparing, laparoscopic |
| Modified gastrectomy, type B | Partial gastrectomy, Total resection | D1+lymph nodes along the left gastric artery, lymph nodes along the forward groups along the general hepatic artery, lymph nodes along of celiac artery | no |
| Conventional | Total resection | D2 – removal of lymph nodes corresponding to tumor localization in a stomach, but always 7, 8a, 9, 11 groups; according to indications: lymph nodes of regional groups 10 (UML, UM, U*), 11d (UM, U*), 12a (UML, LD, L, M, ML, MU*), 14v (UML, L, LD*) | no |
| Advanced | Total resection, Extended total resection | D3 – always 8b, 16a2, 16b1, 12b, 12p; according to indications: lymph nodes of regional groups 10 (M, ML*), 11d (M, ML*), 12a (U*), 14v (M, ML, UM*), 19 (UML, MU, U*), 20 (UML, UM, U*), 110,111, 112 (E*) | no |

* Specification of the stomach parts: U – the top third of the stomach, M – within the middle one-third of the stomach, L – the lower third of the stomach, E – esophagus, D – duodenum.

In accordance with the recommendations of the JGCA execution of transactions connected with SC. Thus, in the case of 1A stage the correct radical

procedure could vary from endoscopic mucosa resection to the standard gastrectomy. Therefore, specific operational choice depends on the TNM stage.

1. Stage 1A, T1N1Mo: Endoscopic mucosal resection or modified gastrectomy.

Table 2. Summarized treatment recommendations for 1A stage of SC.

| Invasion depth | Histological type | Tumor size | Type of operation |
|---|---|---|---|
| Mucous | well differentiated tumor | Less 2,0см | Endoscopic mucous resection |
| | | More 2,0см | Modified gastrectomy, type A |
| Mucous | poorly differentiated tumor | - | Modified gastrectomy, type B |
| Submucous | well differentiated tumor | Less 1,5 см | Modified gastrectomy, type A |
| Submucous | poorly differentiated tumor | - | Modified gastrectomy, type B |

Endoscopic resection is indicated for patients with a tumor without the regional lymph nodes involvement. According to JGCA, intestinal SC type with localization in mucosa, the size of less than 2 cm to be considered has no metastases in regional lymph nodes. Endoscopic single block resection of the stomach mucosa has certain advantages, but because of the high risk of recurrence after endoscopic resection 2 cm is the limiting threshold for this operation. Clear assessment of invasion depth, histological phenotype and size of the tumor is obligatory for endoscopic operation. In the case of mucous limited SC does not satisfy those requirements, modified gastrectomy or subtotal resection of the stomach, type A (MG-A) should be performed. MG-A also indicated in the case of well-differentiated gastric cancer less than 1.5 cm in diameter. In the case of submucosal SC, meets these requirements, modified gastrectomy or subtotal resection of the stomach, type B in (MG-B) should be done.

In the case of the lower third of the stomach to remove 8A groups of lymph nodes (front upper panel along the common hepatic artery) is not shown.

2. Phase 1b, T1N1Mo, T2NoMo

Modified type of gastrectomy or standard gastrectomy are indicated for the 1B stage of SC depending on case T and N categories. It is considered in the presence of T1N1Mo tumor lesser than 2.0 cm in diameter, performing modified type of gastrectomy is preferable. In the presence of T1N1Mo tumor larger than 2.1 cm or meets the criteria T2NoMo, typical gastrectomy is acceptable. Table 3 summarizes treatment recommendations for 1B stage.

Table 3. Algorithm of treatment of SC in 1B.

| Invasion depth | Tumor size | Lymph nodes involvement | Type of operation |
|---|---|---|---|
| T1 (mucous, submucous) | Less 2,0см | N1 | Modified gastrectomy, type B |
| T1 (mucous, submucous) | 2,1 cm and more | N1 | Standard gastrectomy |
| T2 (own muscular cover, subserous) | 2,1 cm and more | No | Standard gastrectomy |

3. Stage 2, T1N2Mo, T2N1Mo, T3NoMo

Standard gastrectomy is indicated for 2$^{nd}$ stages of SC, regardless of T and N categories. Table 4 lists treatment recommendations stage 2 SC.

Table 4. The algorithm of treatment for stage 2 SC.

| Depth of invasion | Lymph nodes involvement | Type of operation |
|---|---|---|
| T1 | N2 | Standard gastrectomy |
| T2 | N1 | Standard gastrectomy |
| T3 | No | Standard gastrectomy |

Adjuvant chemotherapy is recommended since 2$^{nd}$ stage of SC, however even till now there is no approved treatment guidelines for postoperative adjuvant chemotherapy. It is necessary to conduct clinical studies to confirm the standard mode of adjuvant of treatment in SC.

4. Stage 3a, T2N2Mo, T3N1Mo, T4NoMo

Standard or extended GE are preferable for stage 3A SC depending on T and N categories, as it is shown in the table. Table 5 summarizes treatment recommendations 3A stage SC.

Table 5. The algorithm of treatment stage 3A SC.

| Depth of invasion | Lymph nodes involvement | Type of operation |
|---|---|---|
| T2 | N2 | Standard gastrectomy |
| T3 | N1 | Standard gastrectomy |
| T4 | No | Advanced gastrectomy |

It is necessary to conduct clinical research at this stage of the SC in order to establish precise indications for adjuvant treatment. In the case of T4 combined resection of involved adjacent structures and/or the adjuvant radiotherapy might be indicated in order to reduce potential risk of residual tumor arising.

5. Stage 3B, T3N2Mo, T4N1Mo

Standard or extended GE indicated in stage 3B of SC, according of T and N indexes, as it is shown in the following table. Although the effect of D3 lymph node dissection as a surgical intervention for N2 tumors is not totally clear yet, the D3 has been frequently utilizing in routine practice in Japan [5]. Novel treatment recommendations for stage 3B SC management are listed in the table #6.

Table 6. The algorithm of treatment stage 3B, RJ.

| Depth of invasion | Lymph nodes involvement | Type of operation |
|---|---|---|
| T3 | N2 | Standard gastrectomy |
| T4 | N1 | Advanced gastrectomy |

Multiple organ resections in the case of neighbor organ involvement are indicated in the T4 SC in order to obtain Ro operation. The issue of adjuvant and neoadjuvant radiotherapy or chemotherapy still remains not fully clarified.

6. Stage 4-N3, CY1, M1.

Most cases of SC 4 stage cannot be radically cured by doing surgery alone, except that the N3 or T4N2Mo tumor. If N3 presence is the sole determining factor

for stage 4, D3 operation might be potentially effective to run Ro resections. Table 7 shows the total Protocol radical surgical treatment of SC.

Table 7. Total treatment protocol when SC [5].

<table>
<tr><td></td><td>No</td><td>N1</td><td>N2</td><td>N3</td></tr>
<tr><td>T1(M)</td><td>IA<br>Endoscopic mucous resection</td><td rowspan="2">IB<br>Modified gastrectomy, type B or<br>Standard gastrectomy</td><td rowspan="2">II<br>Standard gastrectomy</td><td rowspan="5">IV<br>Advanced or palliative gastrectomy,<br>Chemoradiotherapy or Palliative care</td></tr>
<tr><td>T1(SM)</td><td>IA<br>Modified gastrectomy, type A or type B</td></tr>
<tr><td>T2</td><td>IB<br>Standard gastrectomy</td><td>II<br>Standard gastrectomy, adjuvant chemotherapy</td><td>IIIA<br>Standard gastrectomy, adjuvant chemotherapy</td></tr>
<tr><td>T3</td><td>II<br>Standard gastrectomy, adjuvant chemotherapy, adjuvant radiotherapy</td><td>IIIA<br>Standard gastrectomy, adjuvant chemotherapy</td><td>IIIB<br>Standard gastrectomy, adjuvant chemotherapy</td></tr>
<tr><td>T4</td><td>IIIA<br>Advanced gastrectomy, adjuvant chemotherapy, adjuvant radiotherapy</td><td>IIIB<br>Advanced gastrectomy, adjuvant chemotherapy, adjuvant radiotherapy</td><td colspan="2"></td></tr>
<tr><td>M1</td><td colspan="4">IV</td></tr>
</table>

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.

**The aim** of the work was to compare the influence of different operation types to survival of our patients.

## 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 8.

Table 8. 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 [10] with the formation of the anti-reflux terminal-lateral mufti-like retro-colic esophago-jejunum 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 considered as an adjacent for stomach structures [4]. 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%).

Survival rate of our patients has been studied. Statistic calculations were carried out using ANOVA (analysis of variance) by implementing the statistical program SSP set to evaluate the strength of the correlation between the groups utilizing the linear correlation coefficient by Pearson. To assess the credibility of different groups – coefficient Wilcockson test has been utilized. Comparison of survival by Cox regression is not reasonable. It was estimated the cumulative duration of lifespan after treatment, evaluated in months (absolute numbers).
The conclusions were made by p Wilkockson 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 9.

Table 9. 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 #10.

Table 10. 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 ± 0,9 | 90 |
| 2. Radical | D 2 | 31,6 ± 0,7 | 65 |
| 3. Advanced gastrectomy | D 3 | 37,9 ± 0,9 | 33 |

Each removed tissue have examined histologically. Distribution of distant lymph node groups by JGCA classification began to do recently. Removed lymph nodes have been ranked in 7 groups: paragastric of large curvature (# 4-6), paragastric 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 hemipancreatosplenectomy 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 11.

Table 11. Distribution of gastric cancer patients in stages as a percentage.

| 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 pT2bN3Mo | | | 3 | 1,59 |
| | 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 12 presents the characteristics of patients according to the degree of the local prevalence of SC.

Table 12. 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 |

In cases when tumor has a large and (or) small epiploon, gastro-colic ligament (or) gastro-hepatic ligament, spreading into the muscular layer of the stomach wall, without perforation of the visceral peritoneum, the tumor has been classified as T2. In 4 cases, the tumor perforates visceral peritoneum, which covers the ligaments of stomach or epiploon has been classified as T3.

According to the TNM classification of 6 regional lymph nodes were located along the small and the large curvature, left gastric, hepatic and splenic artery, splanchnic trunk and hepato-duodenal.

No-there are no signs of regional lymph nodes in the study at least 15 delivered the lymph nodes;

N1-metastasis in 1-6 regional lymph nodes;

N2-metastasis in 7-15 regional lymph nodes;

N3-metastasis to more than 15 lymph nodes.

Distant metastases were classified as standard, as Mo – in the absence of distant metastases and M1-defined – in the presence of distant metastases. Retroperitoneal metastases in lymph nodes, as mentioned above, also attributed to category M1.

Histopathological grading (G):

G1-highly differentiated tumor;

G2- moderately differentiated tumor;

G3- poorly differentiated tumor

G4: undifferentiated (anaplastic) a tumor.

Gx- degree of tumor differentiation.

In table 13 presents the characteristics of the patients according to the degree of differentiation SC.

Table 13. The distribution of patients with tumor differentiation of SC.

| Histopathological grading | Number of patients | Percentage |
|---|---|---|
| G1 | 5 | 2,66 |
| G2 | 86 | 45,75 |
| G3 | 80 | 42,55 |
| G4 | 17 | 6,92 |

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 perinevral invasion (Nev) [6], the presence of residual tumor tissue (R).

The degree of vascular (v, a venous and lymphatic, ly) involvement by JRSGC [5]:

- 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 preparates by hematoxylin-eosin (H&E), while according to the literature [5] 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 (venules 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 14 shows the distribution of SC in stages depending on the presence of tumor emboli (OE).

Table 14. 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%** |

## The results obtained

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 15.

Table 15. 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 [7]. 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.

In examining cross-dependence correlation of stage and the absence of OE in these microvessels $R_{Vo}$ = 0.59 (SEE = 1.35, p = 0.038) and almost complete independence in the interaction between of tumor stage and OE: R = 0.42 (SEE = 1.59, p = 0.083). This conclusion was totally unexpected, statistical error probability evaluation was 1.59. Thus, this allows us to consider SC as a primarily haematogenously-disseminated disease. This conclusion is confirmed by the studying correlation of prevalence the sign in the stage. A significant involvement of microvessels most often met in $2^{nd}$ and $3^{rd}$ stages. Tumor emboli were already present in stage 1B, i.e. rT1N1Mo, rT2aNoMo, rT2bNoMo stages. To control this thesis the circulating in the bloodstream of malignant cells study is essential.

Lack of microvessels involvement also correlates the perinevral growth deficiency: R = 0.98 (SEE = 4.41, p = 0.0001), highlights the complete absence of correlation between the perinevral and perivasal growth: R = 0.21 (SEE = 25.35, p = 0.178). Indeed, the perinevral growth is a variant of the local growth of tumor tissue, indicating the proliferative potential of SC. At the same time, perivasal growth characterizes metastatic potential ability of hematogenic dissemination.

High close to absolute, the direct relationship between Vo and the absence of residual tumor tissue Ro (R = 0.95, SEE = 6.46, p = 0.0005) characterizes by tumors, regardless of the stage had no propensity to metastasize hematogenic. Such tumors better respond to surgical intervention. It is in this group lymph node

dissection for SC provide positive results. Extremely high negative correlation absence of perivasal growth and microscopically detected residual tumor tissue R1 (R = 0.97, SEE = 4.67, p = 0.0001) indicates the same. The absence of indirect signs of hematogenic dissemination in 4th stage in 35.64 percent manifests about the positive perspective of lymph node dissection even at the advanced stage. The 4 – stage tumors were rTanyN3Mo, i.e. nearly 40% of the SC did not have perivasal growth even if 15 regional lymph nodes involved. The same can be said of 36 patients with tumors that have stage 3A histological phenotype rT2a-2bN2Mo and rT3N1Mo. 5 patients with metastases in the lymph nodes, 15-7 and 31 patient with 1-6 affected regional lymph nodes did not have perivasal growth on histological examination.

In the second stage, characterized by the presence of phenotypes rT1N2Mo, rT2aN1Mo, rT2bN1Mo, rT3NoMo, 7 patients with SC had a significant vascular lesion. In spite of this, the survival rate after radical treatment in this group of patients was 34.1 of the month, an average survival rate of these patients was about 3 years. The survival of patients after D3 in 2 stages of SC – 48 months, after D2 – 20.3 months and 34 months after the standard resection of the stomach and gastrectomy. However, in the absence of perivascular growth when D1 lymph node dissection patients lived in 2 stages approximately 32 months, perivascular growth presence – 24 months, when V + tumors combined with D2 lymph node dissection 18.5 months when performing standard operations – 24 months. There was revealed a high correlation between the survival of patients with perivascular growth present and three other indicators. No. 1-the survival of patients with tumors G1\G2 SC (R = 0.87, p = 0.4, SEE = 3.7). No. 2-the survival of patients with Ro-operations (R = 0.8, p = 0.0000, SEE = 3.95). No. 3-relationship with the survival of patients with tumors with Nev\0 phenotype (R = 0.89, p = 0.0000, SEE = 3.05). Regardless of the stage, perivascular growth presence was directly linked to the perinevral spread of tumors – R=0.83. Inverse proportionality with strong perivascular growth has been observed in the absence of perinevral growth and Ro – resections. I.e. the more perivascular growth was expressed, the less likely Ro-resection could be done, and vice versa.

The more there is, the more often the perivascular growth was, etc. In the study of life expectancy is not dependent on the stage and type of performed operation duration of observation About patients, 23.6 ± 5.6 months, not statistically different from the duration of the observation of the V1, 19.2 ± 5.6 months (p = 0.25, F = 129). Traced the influence of type of operation performed on the life expectancy of patients depending on the presence of perivascular growth. So the D3 dissection increased the survival rate of patients with SC in Vo 1A and 3A, V1-2 SC patients, 3A, 4 stages. The advantage of pliable distal tip advances

easily over D1 D2 by the criterion of duration of observation of the patients mentioned in the Vo patients SC in 3A and 4 stages, with V1-3A.

Perinevral growth research depends on the type of operations, duration of patient follow-up, the number of removed lymph nodes, degree of tumor differentiation. Table 16 shows the distribution of SC patients in stages, depending on the availability of perinevral tumor infiltration.

Table 16. The distribution of patients in stages, depending on the availability of microscopically by perinevral growth.

| Stage | Perinevral growth | | | | Ratio of occurrence of a sign in a stage |
|---|---|---|---|---|---|
| | No | | N1 | | |
| | Absolute values | Percentage | Absolute values | Percentage | |
| 1A | 1 | 0,53% | 0 | 0% | 0% |
| 1B | 13 | 1,59% | 1 | 0,53% | 7,14% |
| 2 | 6 | 3,72% | 8 | 3,72% | 57,14% |
| 3A | 55 | 29,26% | 5 | 2,66% | 8,33% |
| 3B | 13 | 6,91% | 1 | 0,53% | 7,14% |
| 4 | 80 | 42,55% | 5 | 2,66% | 5,88% |
| Sum | 168 | 89,36% | 20 | 10,64% | **10,64%** |

20 of 188 examined histological preparations had signs of perinevral invasion, as an early sign of high potential of early local relapse of SC and potential of perinevral tumor generalization. An unusually high percentage of perinevral growth in 2nd stag seems to be due to the fact that 9 out of 14 patients had rT3NoMo phenotype. Total cross-linkages between criteria G, V, R, Nev, as well as the stage of SC, type of lymph node dissection and survival is shown in table 17.

Table 17. Cross connection between criteria G, V, R, Nev., as well as the stage of SC, depth of completed lymph node dissection and survival.

| | G1\G2 | G3\G4 | Vo | V1 | Ro | Nev\0 | Nev\1 | Stage ST | Type of op |
|---|---|---|---|---|---|---|---|---|---|
| G1\G2 | - | - | **R=0,87** p=0,4 SEE=3,7 | R=0,2 p=0,0001 SEE=9,1 | **R=0,79** p=0,27 SEE= | **R=0,9** p=0,0000 SEE=3,2 | R=0,14 p=0,1 SEE=9,41 | R=0,28 p=0,03 SEE= | **R=0,6** p=0,0024 SEE=4,7 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 4,7 | | | 8,66 | |
| G3\G4 | - | - | R=0,18 p=0,08 SEE=11,5 | R=0,37 p=0,01 SEE=10,1 | R=0,06 p=0,2 SEE=12,3 | R=0,1 p=0,15 SEE=12,0 | R=0.0006 p=0,47 SEE=12,7 | R=0,23 p=0,05 SEE=11,2 | R=0,03 p=0,3 SEE=12,1 |
| Vo | **R=0,87** p=0,4 SEE=3,7 | R=0,18 p=0,08 SEE=11,5 | - | - | **R=0,8** p=0,0000 SEE=3,95 | **R=0,89** p=0,0000 SEE=3,05 | R=0,12 p=0,13 SEE=8,57 | R=0.3 p=0,03 SEE=7,6 | R=0,38 p=0,02 SEE=4,1 |
| V1 | R=0,2 p=0,0001 SEE=9,1 | R=0,37 p=0.01 SEE=10,1 | - | - | R=0,12 p=0,13 SEE=10,4 | R=0,11 p=0,13 SEE=10,4 | R=0,3 p=0,03 SEE=9,36 | R=0,19 p=0,08 SEE=9,96 | R=0,13 p=0,23 SEE=9,1 |
| Ro | **R=0,79** p=0,27 SEE=4,7 | R=0,06 p=0,2 SEE=12,3 | **R=0,8** p=0,0000 SEE=3,95 | R=0,12 p=0,13 SEE=10,4 | - | **R=0,89** p=0,0000 SEE=2,84 | R=0,09 p=0,15 SEE=7,97 | R=0,19 p=0,06 SEE=7,5 | **R=0,96** p=0,0000 SEE=0,83 |
| R1 | R=0,0002 | R=0,0003 p=0,5 SEE=12,7 | R=0,0001 p=0,5 SEE=9,1 | R=0,05 p=0,22 SEE=10,7 | - | R=0,01 p=0,38 SEE=16,1 | R=0,14 p=0,1 SEE=14,9 | R=0,19 p=0.37 SEE=14,6 | R=0,12 p=0,32 SEE=15,6 |
| Nev\0 | **R=0,9** p=0,0000 SEE=3,2 | R=0,1 p=0,15 SEE=12,0 | **R=0,89** p=0,0000 SEE=3.05 | R=0,11 p=0,13 SEE=10,4 | **R=0,89** p=0,0000 SEE=2,84 | - | - | R=0,25 p=0,04 SEE=8,62 | **R=0,82** p=0,0000 SEE=2,9 |
| Nev\1 | R=0,14 | R=0,0006 | R=0,12 | R=0,3 p=0,0 | R=0,09 | - | - | R=0,0009 | R=0,005 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | p=0,1 SEE= 9,41 | p=0,4 7 SEE= 12,7 | p=0,1 3 SEE= 8,57 | 3 SEE= 9,36 | p=0,1 5 SEE= 7.97 | | | p=0,4 6 SEE= 11,9 | p=0,4 2 SEE= 11,7 |
| Type of op | **R=0,6** p=0,0 024 | R=0,0 3 p=0,3 | R=0,3 8 p=0,0 2 | R=0,1 3 SEE= 9,1 | **R=0,9 6** p=0,0 000 SEE= 0,83 | **R=0,8 2** p=0,0 000 SEE= 2,9 | R=0,0 05 p=0,4 2 SEE= 11,7 | R=0,0 3 p=6,2 9 | - |

Index R is the numeric value of coefficient of Pearson linear correlation, p-reliability, SEE-the standard error of calculations. Absence of perinevral growth in the study was the most sensitive factor with direct correlation, which is close to 1.0 in relation to the absence of perivasal 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 perivasal growth as well as residual tumor tissue presence.

The presence of perinevral 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 perinevral 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 $2^{nd}$ and $3^{rd}$ stages. The advantage of lymph node dissection at Nev\0 in $4^{th}$ stage were not statistically proved. In the perinevral tumor growth present, that is Nev/1, D3 dissection has had a positive effect on the survival rate in $2^{nd}$ and $3^{rd}$ 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 perinevral 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, perinevral growth believed to be the negative predicting factor. Table 18 shows the distribution of patients in stages, depending on the availability of R1.

Table 18. 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 dissemated 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 perinevral 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 (R = 0.98, SEE = 4.41, 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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