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CLINICOPATHOLOGICAL FEATURES OF SIEWERT TYPE II ADENOCARCINOMA OF THE ESOPHAGOGASTRIC JUNCTION AND LONG-TERM OUTCOMES OF RADICAL SURGERY TREATMENT

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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy in Medicine

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GENERAL DESCRIPTION OF THE RESEARCH

Relevance of the topic: Despite a slow decline in the morbidity frequency of gastric cancer, a threefold increase in the incidence rate of adenocarcinoma of the esophagogastric junction (EGJ) in Western countries over the last 40 to 50 years has been observed [Buas M.F. and Vaughan T.L., 2013; Cellini F. et al., 2014][1,2,3].

Although different classifications have been used to differentiate the clinical and anatomical types of EGJ, the most widely used classification in clinical oncology today is the Siewert classification. [Zanoni A., 2017][3]. According to this classification, EGJ is divided into 3 types - Siewert type I, Siewert type II, and Siewert type III. Type I: The epicenter of the tumor is located 1.0-5.0 cm proximal to the anatomical cardia and adenocarcinoma infiltrates proximally the esophagogastric junction. Type II: The epicenter of the tumor is located 1.0 cm proximal 2.0 cm distal to the anatomical cardia and adenocarcinoma develops from the short-segment intestinal metaplasia zone of the esophagogastric junction. Type III: The epicenter of the tumor is located 2.0-5.0 cm distal to the anatomical cardia and adenocarcinoma infiltrates distally the esophagogastric junction As noted above, although EGJ was accepted as a separate oncologic unit according to the TNM classification in 2010, and treatment strategies of esophageal cancer and gastric cancer were analyzed separately in ESMO Protocol adopted on carcinoma of the upper gastrointestinal tract in 2018, the treatment strategy for EGJ was not addressed as a free oncological unit [ESMO, 2018].

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[1]Buas, M.F. and Vaughan, T.L. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease//Semin Radiat Oncol,- 2013: 23,- pp.3-9.

[2]Cellini, F. Clinical management of gastroesophageal junction tumors: past and recent evidence for the role of radiotherapy in the multidisciplinary approach / A.G. Morganti, F.M. Di Matteo [et al] // Radiation Oncology, - 2014: 9, - pp.45-55.

[3]Zanoni, A. How to Treat EGJ Cancer: Indications and Treatment Strategy. In: Giacopuzzi S., Zanoni A., de ManzoniG.(eds) / S. Giacopuzzi, S Laiti., Di Leo A.Di Leo, de Manzoni G.// Adenocarcinoma of the Esophagogastric Junction. Springer,-2017: pp. 117-137.

These arguments can also be seen as an indirect manifestation of the lack of standardization of treatment tactics for EGJ and the lack of consensus on it. Thus, the above suggests that EGJ is becoming a growing clinical and oncological problem, and as with other types of adenocarcinomas, there are controversial opinions about the clinical and pathological features and treatment tactics of Siewert type II adenocarcinoma. We consider it necessary to conduct special research in this direction in order to clarify this and some similar contradictions.

Research object: The objects of the present study were patients who underwent radical surgery for Siewert type II EGJ at the Oncology Clinic of the Azerbaijan Medical University from July 2007 to December 2016. During the mentioned period, 343 patients underwent radical surgery with gastric and esophageal cancer. EGJ was confirmed in 218 of these patients. In 122 of the latter patients, radical surgery was performed for Siewert type II EGJ.

The purpose of the research*:* The research aimed to improve the outcome of the treatment of relevant patients by a comparative study of the clinical and pathological features of Siewert type II adenocarcinoma of the esophagogastric junction and the long-term outcomes of radical surgery.

The tasks of the research:

1. Study of clinical and pathological features of Siewert type II adenocarcinoma of the esophagogastric junction and areas of lymphogenic metastasis;
2. Study of the pathological changes in the esophagus and gastric mucosa, not damaged by cancer in Siewert type II adenocarcinoma of the esophagogastric junction;
3. Determination of the presence of H.pylori in the gastric mucosa during Siewert type II adenocarcinoma of the esophagogastric junction;
4. Comparative analysis of long-term outcomes of transhiatal extended gastrectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction;

5. Determination of the optimal volume of lymphodissection in Siewert type II adenocarcinoma of the esophagogastric junction;
6. Study of the effectiveness of neoadjuvant and adjuvant chemotherapy in Siewert II adenocarcinoma of the esophagogastric junction;

Research methods:

All patients with Siewert II adenocarcinoma of the esophagogastric junction were diagnosed based on endoscopy and pathohistological examination of the bioptant. Resectionability of the process was determined using upper abdominal CT in all patients. All patients underwent chest radioscopy and 78 patients underwent abdominal parenchymatous ultrasonography. General blood analysis, biochemical analysis of blood consisting of functional indicators of liver and kidneys were performed. CEA titers of the blood plazma were determined in 46 patients before surgery.

Main points presented to the defense of the dissertation:

1. EGJ is a free oncological unit with distinctive features in terms of the relationship of Siewert type II adenocarcinoma with H. Pylori and metaplasia of the surrounding mucosa.
2. Siewert type II EGJ has different pathomorphological features from gastric cancer, including different lymphogenic metastasis.
3. Due to specific localization and clinical-pathological features of Siewert type II EGJ, different surgical approaches are required for Siewert type II EGJ and gastric cancer.
4. Localization of Siewert type II EGJ, characteristic biological and pathomorphological features, different lymphogenic metastases lead to different volumes of extended lymphodissection.
5. Extended gastrectomy performed using transabdominal-transhiatal approach in Siewert type II EGJ can provide oncological radicalism.
6. Based on preoperative examinations, it is possible to convert Siewert type II EGJ, which is assumed to be locally

unresectable, to a resectable state by means of neoadjuvant chemotherapy in some patients.

7. Adjuvant chemotherapy is able to prolong the life of patients with T2-4 stage Siewert type II EGJ

Scientific novelty of the research. Some aspects of the specificity of the clinical and pathological features of Siewert type II adenocarcinoma of EGJ have been identified. Significant results have been achieved in solving the problem of choosing the optimal approach and volume of the radical surgical treatment of patients with appropriate cancer. Besides, significant results were obtained on the clinical and pathological features of Siewert type II EGJ, and the effect of neoadjuvant and adjuvant chemotherapy on the survival rates of patients. Based on the results obtained, a treatment algorithm was developed that reflects the multimodal treatment tactics of the respective patients.

Practical significance of the research. The results of the study will be important not only for gastrointestinal oncologists but also for gastroenterologists. The practical application of the findings will reduce the risk of postoperative complications, mortality rate, and increase survival rates of relevant patients.

Application of the research work. The results of the research are used in the diagnosis and treatment of relevant patients in the Thoracoabdominal Surgery Department of the Oncology Clinic of the Azerbaijan Medical University. Moreover, some points of the dissertation were included in the relevant topics of the training program on the oncology subject for the 5th and 6th year students of the Treatment-prevention faculty of the Azerbaijan Medical University.

Published scientific works. Eight articles and ten theses on the topic of the dissertation have been published.

Approbation and application of the dissertation work .

The materials of the dissertation were discussed at the ESMO 17th World Congress on Gastrointestinal Cancer (Spain, Barcelona, July 2015); The 18th ECCO – 40th ESMO European Cancer

Congress (Austria, Vienn, September 2015); The ESMO 18th World Congress on Gastrointestinal Cancer (Spain, Barcelona, June 2016); The 41st ESMO Congress (Denmark, Copenhagen, October 2016). The dissertation was primarily discussed at the joint meeting of the researchers of the Departments of Oncology, and the 3rd Surgical Clinic of the Azerbaijan Medical University and Oncology Clinic of the Azerbaijan Medical University, held on 09.01.2019 (Baku,2019) and at the Scientific Seminar of the FD 1.02 Dissertation Council operating under National Oncology Center on 15.04.2021 (protocol № 2) (Baku, 2021).

Name of the organization where the dissertation work was performed: The dissertation work was carried out at the Oncology Clinic of the Azerbaijan Medical University.

Volume and structure of the dissertation. The dissertation consists of 136 pages of computer typing (229,449 characters), including introduction (13,582 characters), I chapter (45,190), a description of research materials and methods (25,201characters), tree chapters commenting results of the research (24,477+35,019+35,795 characters), discussion of the results, conclusions, practical recommendations (44,288 characters) and a reference list. The results of the dissertation are presented in 11 tables and 19 figures. The reference list consists of 163 (10 local, 153 foreign) sources, most of which are in English and a small number in Russian, covering the research of the last 5-10 years.

MATERIALS AND METHODS OF THE RESEARCH

Contingent of the research. The objects of the present study were patients who underwent radical surgery for Siewert type II EGJ at the Oncology Clinic of the Azerbaijan Medical University from July 2007 to December 2016. During the mentioned period, 343 patients underwent radical surgery with gastric and esophageal cancer. EGJ was confirmed in 218 of these patients. In 122 of the

latter patients, radical surgery was performed for Siewert type II EGJ.

In accordance with the purpose of the study, the results of the examinations were analyzed retrospectively and prospectively, and patients were divided into groups according to the Siewert classification. As seen in Table 1, 122 (69.7%) of the patients had Siewert type II EGJ.

Table 1

Distribution patterns of EGJ in patients according to Siewert types

Age groups	Siewert I		Siewert II		Siewert III	
	Male	Female	Male	Female	Male	Female
≤50	1(4.2±1.3)	0	14(14.6±2.4)	4(15.4±2.4)	7(13.5±2.3)	4(28.6±3.1)
50-70	17(70.8±2.5)	6(100.0±0.0)	74(77.1±2.8)	20(76.9±2.8)	42(80.7±2.7)	10(71.4±3.1)
>70	6(25.0±2.9)	0	8(8.3±1.9)	2(7.7±1.8)	3(5.8±1.6)	0
Total	24(11.0±2.1)	6(2.8±1.1)	96(44.1±3.4)	26(11.9±2.2)	52(23.8±2.9)	14(6.4±1.6)
218	30(13.8±2.3)		122(56.0±3.4)		66(30.2±2.9)	

The pathological and anatomical characteristics of Siewert type II EGJ are described in Table 2. As seen in the table, the majority of patients who underwent radical surgery (78.0%) consulted a doctor at the stages T4a (T3 according to the 6th edition of the TNM classification) and T4b (T4 according to the 6th edition of the TNM classification). Patients with metastasis of adjacent organs accounted for 18.0% of the corresponding patients. In the early stages of cancer, the tumor process was detected in only 3.3% of patients. According to the 7th edition of the *AJCC / UICC TNM classification (2010), T is deliberately grouped together with T2 because it implies invasion to the subserous layer T3.

Table 2

Pathological and anatomical characteristics of Siewert type II EGJ

T stage	N0	N 1	N2	N3	Total
T1	4(10.5±2.8)	0	0	0	4(3.3±1.6)
T2-T3*	11(32.4±4.2)	8(34.8±4.3)	4(16.0±3.3)	0	23(18.9±3.3)
T4a	15(44.1±4.5)	11(47.8±4.5)	16(64.0±4.3)	31(77.5±3.8)	73(59.8±4.4)
T4b	4(10.5±2.8)	4(17.4±3.4)	5(20.0±3.6)	9(22.5±3.8)	22(18.0
Total	34(27.9±4.1)	23(18.9±3.5)	25(20.5±3.7)	40(32.7±4.2)	122

In all patients, the type of adenocarcinoma was confirmed according to the Siewert classification based on the macroscopic examination of the resectant as a more accurate and decisive method. The proximal edge of the resectant, the gradation of the adenocarcinoma, and the depth of transmural spread were examined under a light microscope by the same experienced pathologist using the traditional hematoxylin and eosin staining method. The average number of taken lymph nodes was 21 (16-28).

Lymph nodes were numbered according to the classification of the Japanese Research Society for Gastric Cancer (JRSGC) [Kajitani T., 1981][4] and sent for pathohistological examination with a resectant. Lymph nodes were prepared separately in the pathohistological laboratory and examined under a light microscope after staining 7-8 μm sections with hematoxylin and eosin according to generally accepted procedures.

The stage of cancer according TNM was established based on the 7 th edition of the AJCC / UICC classification. Extended proximal gastric resection with the left thoracoabdominal approach,dissection of D2+lower mediastinal lymph nodes was performed on 3 patients

[4] Kajitani, T.Japanese Research Society for gastric cancer.The general rules for the gastric cancer study in surgery and pathology. Part I.Clinical classification//Jpn Surg,-1981, 11.-pp.127-139.

with Siewert type II EGJ; Extended proximal gastric resection with the transabdominal approach, dissection of D2+lower mediastinal lymph nodes on 2 patients;Transthoracic gastrectomy on 6 patients (with the left thoracoabdominal approach), dissection of D2+lower mediastinal lymph nodes; Extended gastrectomy with a transhiatal approach, dissection of D2+lower mediastinal lymph nodes was performed on 111 patients.

Gastrectomy on 22 patients, multiorqan resection was performed (gastrectomy, left lateral segmentectomy of the liver, extensive resection of the tendon of the diaphragm left part ; splenectomy; gastrectomy, peripheral resection of segments III and IV of the liver; gastrectomy, distal pancreatosplenectomy; gastrectomy, peripheral resection of the pancreas) due to merastasis in adjacent organs (liver, diaphragm, spleen, pancreas).

Extented lymphodissection was performed in all patients who underwent multiorgan resection. In two patients, due to multifocal cancer (respectively, because the second tumor was located in the small intestine and in the middle third of the esophagus), gastrectomy and small bowel resection were performed, respectively; Lewis resection of the esophagus and reconstruction with a pipe made of the greater curvature of the stomach were performed. All patients were diagnosed based on endoscopy and pathohistological examination of the biopsy.

Statistical methods used in the analysis of the material: The difference between the quality indicators was determined by calculating Pearson's criterion $\chi 2$.

$$\chi^2 = n\left(\sum^{a \times b} \frac{x^2}{x_a \cdot x_b} - 1 \right.$$

where *a* is the number of rows in the case table, *b* is the number of columns in the case table, *x* is the frequency of the symptoms in each cell of the table, x_a is the frequency of the symptoms in the corresponding

row, x_b is the frequency of the symptoms in the corresponding column, n is the total frequency of the symptoms.

Patient survival rates were calculated using the Kaplan-Meier estimator, and the difference between the survival rates of the groups was assessed using a log-rank test. Patients, who are currently living and under observation are considered censored, and patients, who have been lost for a period of time during the study period, are uncensored.

The above calculations of the mean value (M), the standard deviation of the average value (SD) were performed with SPSS 10.0 version (SPSS, Chicago, Illinois, USA) designed for Windows program. A value of the probability P less than 0.05 was considered statistically reliable.

Results and Discussion of the Research

We studied Siewert type II EGJ (the Lauren classification of adenocarcinoma) in comparison with Siewert type I, Siewert type III adenocarcinoma, and gastric cancer. As a result of the analysis, we found that Siewert type II EGJ had diffuse type in 58.2% of cases and histoarchitectonics of intestinal type of cancer in 41.8% of cases (Table 3). The mentioned types amounted to 20.0 ± 3.6% and 80.0 ± 3.6% ($t = 11.8$; $p < 0.001$) for Siewert type I EGJ, respectively, and 60.6 ± 4.4% and 39.4%± 4.4% for Siewert type III EGJ, respectively ($t = 3.4$; $p > 0.05$). The types of gastric cancer according to the Lauren classification amounted to 32.8 ± 4.3% and 67.2 ± 4.3%, respectively ($t = 5.7$; $p < 0.001$). Thus, as a result of our mathematical analysis, we found that there was no significant difference between Siewert type II EGJ and Siewert type III EGJ. However, Siewert type I EGJ and gastric cancer showed significantly different course from Siewert type II EGJ according to this parameter ($p < 0.001$ and $p < 0.001$, respectively). In other words, the mentioned histoarchitectonics was observed in 41.8±4.5% of the cases of the intestinal-type adenocarcinoma, in 80.0±3.6% cases of Siewert type II EGJ and in 67.2±4.3% cases of gastric cancer. Since esophagogastric adenocarcinoma with intestinal-type histoarchitectonics is associated with a long-term chronic disease, it indicates the less role of chronic diseases in the development of Siewert type II EGJ compared with Siewert type III EGJ and gastric cancer.

Table 3

Comparative description of the pathomorphological features of cancer, gastric and esophageal mucosa in patients with Siewert type II adenocarcinoma

Types of adenocarcinoma according to the Lauren classification	Siewert type I n=30	Siewert type II n=122	Siewert type III n=66	Gastric cancer n=122
Diffuse Intestinal	6 (20.0±3.6) 24 (80.0±3.6)	71 (58.2±4.5%) 51 (41.8±4.5%)	40 (60.6±4.4%) 26 (39.4±4.4%)	40 (32.8±4.3%) 82 (67.2±4.3%)
Gradation of adenocarcinoma G1-2 G3-4	 19 (63.3±4.4) 11 (36.7±4.4)	 21 (17.2±3.4%) 101(82.8±3.4%)	 14 (21.2±3.7%) 5 2(78.8±3.7%)	 33 (27.0±4.0%) 89 (73.0±4.0%)
Metaplasia of the esophageal mucosa	5/5 (100%)	8/27(29.6±4.1%)	2/10(20.0±3.6)	2/10 (20.0±3.6)
Intestinal metaplasia of the gastric mucosa	1/5 (20.0±3.6)	11/27(40.7±4.4)	2/10(20.0±3.6)	11/16(68.7±4.2)
H. Pylori infection of the gastric mucosa	1/5 (20.0±36)	8/27 (29.6±4.1)	2/10(20.0±3.6)	9/16 (56.3±4.5)

Thus, since this cancer has different pathomorphological features, it is confirmed to be a different oncological unit [Huseynova S.E., 2017; Bayramov R.B.; Huseynova S.E.; Abdullayeva R.T., 2017][5,6].

According to the goals and tasks of the study, 5 patients with Siewert type I EGJ, 27 patients with Siewert type II EGJ, 10 patients with Siewert type III EGJ, and 16 patients with gastric cancer were examined for the establishment of the presence of metaplasia of the esophageal mucosa (this sign was examined in10 patients with gastric cancer), intestinal metaplasia of the gastric mucosa, and H. pylori infection.

[5] Huseynova, S.E. Pathomorphological features of Siewert type II adenocarcinoma of the esophagogastric junction // - Baku: Journal of Surgery, - 2017.№; 4, -pp.51-53.

[6] Bayramov, R.B. Pathological characteristics of Siewert's type esophagogastric function adenocarcinoma/S.E. Huseynova, R.T. Abdullayeva //Annals of Oncology,-Barcelona, Spain: 28 June-1 July, 2017. Volume 28, Issue suppl 3, -pp. 017.

Glandular metaplasia in the esophageal mucosa was found in 29.6% of the patients with Siewert type II EGJ whereas, this sign was observed in 20% of the patients with Siewert type III EGJ ($t = 2.3$; $p > 0.05$). However, metaplasia of the esophageal mucosa was found in all patients with Siewert type I EGJ ($t = 2.44$; $p < 0.01$). Thus, as a result of statistical analysis of the results obtained prospectively, we found that unlike Siewert type I EGJ, Siewert type II EGJ is not accompanied by esophageal metaplasia. This indirectly suggests that Siewert type II EGJ does not develop as a result of factors contributing to the development of esophageal metaplasia, but differs significantly from Siewert type I EGJ not only in terms of the histoarchitectonics (58.2 ± 4.5, $29.6 \pm 4.1\%$, $t = 2.6$; $p < 0.001$) and gradation ($17.2 \pm 3.4\%$, $29.6 \pm 4.1\%$, $t = 2.8$; $p < 0.001$) of cancer but also in terms of etiological factor ($p < 0.01$).

Thus, a comparative analysis of a number of pathomorphological features of tumor tissue, esophageal and gastric mucosa in relevant patients suggests that Siewert type II EGJ is a free oncological unit and due to characteristic ecological factors and resulting from these pathomorphological features, it differs significantly from gastric cancer.

In all patients, radical surgery was completed with D2 extended lymphodissection and dissection of the lower mediastinal (region 110) lymph nodes. Dissected lymph nodes were examined one by one by a pathohistologist following the purpose of the study and described separately in the pathological report. By analyzing the frequency of metastatic damage to lymph nodes, the lymphogenic metastasis of Siewert type II EGJ was studied by us following the purpose of the study.

As seen in the table 4, the most common metastatic lesions of the perigastric lymph nodes in Siewert type II EGJ are lymph nodes in the descending order-the 1st (77.9%), 3rd (18.0%), 2nd (11.5%), 5th. (8.2%), 4th (2.5%) zones and no metastasis was observed in the 6th zone lymph nodes.

Table 4.

Frequency of metastatic damage to lymphatic zones in Siewert type II EGJ

Localization	Perigastric, regional and extraregional lymphatic zones												
	1	2	3	4	5	6	7	8	9	10	11	16	110
	Frequency of metastatic damage to lymphatic zones (%)												
Siewert type II	77.9	11.5	18.0	2.5	8.2	0	54.1	5.7	36.9	0	1.6	5.7	3.3

Metastasis was observed in descending order in the 7th (54.1%), 9th (36.9%), 8th (5.7%) and 11th (1.6%) zone regional lymph nodes, and in the 16th (5.7%), and 110th (3.3%) zone extraregional lymph nodes. The size of metastatic lymph nodes was 4-48 mm (average, 12 mm).

In Siewert type II EGJ, the lower mediastinal (zone 110) lymph nodes are exposed to metastatic lesions in a very few numbers of patients (3.3%, based on our results). Rare and exclusive metastatic lesions of these lymph nodes in N3 stage tumors ($p < 0.001$) are indirect evidence of their location above the antegrade lymph flow [Bayramov R.B., Abdullayeva R.T., Huseynova S.E., 2016][7].

As noted, 122 patients underwent radical surgery for Siewert type II EGJ.

We mentioned in Chapter 2 that extended proximal gastric resection with the left thoracoabdominal approach, dissection of lower mediastinal lymph nodes were performed on 3 patients with Siewert type II EGJ, extended proximal gastric resection with the transabdominal approach, dissection of lower mediastinal lymph

[7] Bayramov, R.B. On the frequency of metastatic damage to the mediastinal lymph nodes in Siewert type II adenocarcinoma of the esophagogastric junction / R.T. Abdullayeva, S.E. Huseynova, V.V. Ibrahimov // Materials of the scientific-practical conference dedicated to the 93rd anniversary of National leader H.A. Aliyev, - Baku: - 2016, - pp.43-45.

nodes on 2 patients; transthoracic gastrectomy on 6 patients (with left thoracoabdominal approach), extended gastrectomy with a transhiatal approach was performed on 111 patients. In the latter group of patients, gastrectomy was extended at the expense of the resection of the distal esophagus. During an extended gastrectomy, the distal part of the esophagus was cut 2.6-4.4 cm (on average, 3.0 cm) from the proximal edge of the tumor.

As seen in Table 5, no R2 resection was in any of the patients, although R1 resection was confirmed in only 3 patients, despite an average distance of 3.0 cm (2.6–4.4 cm) from the proximal edge of the tumor. In all other cases (108 patients), R0 resection was considered possible (Table 5).

Table 5.

Pathomorphological characteristics and local recurrence rate of patients underwent extended gastrectomy for Siewert type II EGJ (n = 111)

Parameters	Frequency
Pathomorphological nature of resection R0 resection R1 resection R2 resection	 108 (97.3%) 3 (2.7%) 0 (0%)
Metastasis in the lower mediastinal lymph nodes	3 (2.7%)
Recurrence in the anastomosis area	2 (1.8%)
Suspicious growth in mediastinal lymph nodes based on CT in the long run	0 (0%)

As noted, the lower mediastinal lymph nodes were dissected and purposeful pathohistological examination was performed with all patients who underwent extended gastrectomy. Metastasis to the lower mediastinal lymph nodes was found in only 3 (2.7%) of patients. It should be noted that all three of the latter patients had stage N3 cancer.

As noted above, this suggests that metastatic damage to the mediastinal lymph nodes did not develop directly because they were regional for EGJ, but as a result of extensive lymphogenic metastasis. Thus, the results of the analysis confirmed that the transabdominal-transhiatal approach can provide R0 resection in more than 97% of the patients who underwent extended gastrectomy for Siewert type II EGJ [Huseynova S.E. 2019][8].

The relevant analysis proves that extended gastrectomy performed using the transabdominal-transhiatal approach for Siewert type II EGJ creates adequate conditions to ensure the radicality of the surgical operation and is accompanied by a very low local recurrence rate.

The results suggest that extended gastrectomy performed using the transabdominal-transhiatal approach for Siewert type II EGJ can be considered an adequate radical surgery in terms of oncological radicality. Survival rates after the extended gastrectomy for Siewert type II EGJ and extended lymphodissection for Siewert type III EGJ were comparatively analyzed.

Using the appropriate statistical calculation methods, we determined that the 5-year survival rate after extended lymphodissection for Siewert type II adenocarcinoma was 45.1%, whereas, for Siewert type III adenocarcinoma, the same parameter (Figure 1) amounted to 44.6% (1, 44.6%) ($p > 0.05$).

Thus, the results of the analysis showed no differences in the survival rates after the extended gastrectomy for Siewert type II and extended limphodissection performed for Siewert type III adenocarcinoma. This suggests that extended gastrectomy for Siewert type II EGJ performed by the transhiatal approach may provide adequate radicality in terms of survival.

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[8] Huseynova, S.E. Long-term outcomes of transhiatal extended gastrectomy for Siewert type II adenocarcinoma of the esophagogastric junction // - Baku: Azerbaijan Journal of Oncology, - 2019. No, - pp. 125-128

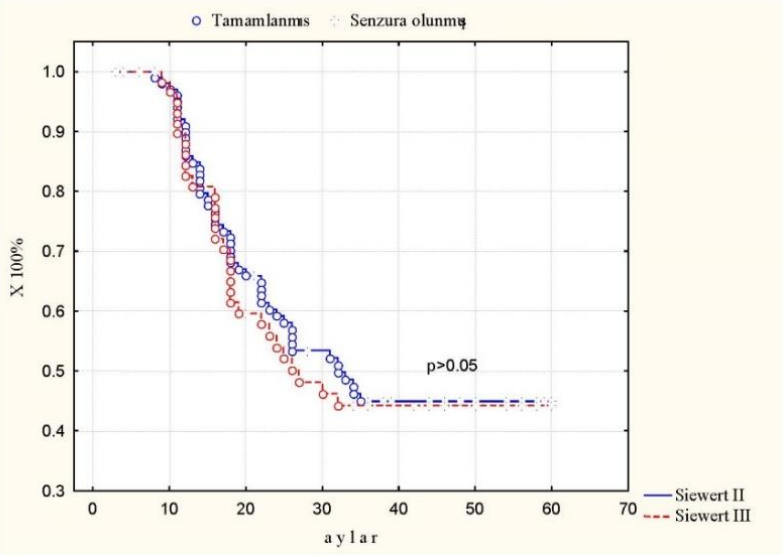

Figure 1. Comparative analysis of survival rates of radical surgeries for Siewert type II and Siewert type III adenocarcinomas.

Thus, according to our research, transhiatal extended gastrectomy for Siewert type II EGJ, D2 lymphodissection, dissection of the lower mediastinal lymph nodes can be considered as a satisfactory surgical operation in terms of adequate removal of the tumor, lymphodissection with adequate volume and long-term outcome, and can be applied as one of the selection operations.

When analyzing the survival rates of patients underwent transabdominal-transhiatal extended gastrectomy for Siewert type II EGJ according to the T stage of cancer (Figure 2), we found that the 5-year survival rate was 48.1% for patients in the T2-T3 stage, 36.2% for the T4a stage, and 46.4% for the T4b stage.

The lower survival rate of the T3 stage compared to other stages was statistically significant ($p<0.05$).

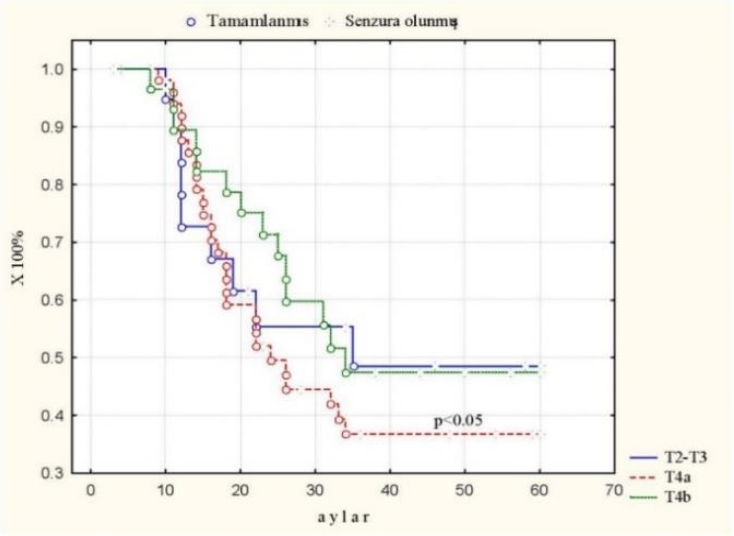

Figure 2. Survival rates of patients who underwent transabdominal-transhiatal extended gastrectomy for Siewert type II EGJ according to stage T cancer. [Bayramov R.B., Huseynova S.E., Abdullayeva R.T., 2016, Bayramov R.B., Abdullayeva. R.T., Huseynova S.E., 2015][9,10]

Although significantly higher survival rates of T2-T3 patients than those of T4a patients are explainable, the high survival rates of T4b patients cannot be substantiated samely and require a different explanation. Multiorgan resection was performed with extended lymphodissection in all patients with Siewert type II adenocarcinoma (stage T4b) spread to adjacent organs.

[9] Bayramov, R.B. Short- and long-term outcomes of multiorgan resection for T4B stage cancer of the proximal third of the stomach / S.E. Huseynova, R.T. Abdullayeva // Journal of Surgery, - Baku: - 2016, No4, - pp. 27-31.

[10] Bayramov R.B. Long-term results following multiorgan resection with extended lymph node dissection for T4b gastric carcinoma / R.T. Abdullayeva, S.E. Huseynova // European Journal of Cancer ECCO 18th, 2281Vienna, Austria,-2015. 25-29 September Vol 51, p 426.

The 5-year survival rate of the patients who underwent multiorgan resection for T4b stage adenocarcinoma with extended lymphodissection was more satisfactory than gastrectomy for T4a stage adenocarcinoma.

This paradoxical result can be explained by the fact that cancer that spread to adjacent organs does not metastasize to distant organs at this stage, which indirectly indicates weak biological aggression of the corresponding carcinoma. To study the efficacy of adjuvant chemotherapy after radical surgery for Siewert type II EGJ, we compared the survival rates of patients who received and those who did not receive appropriate treatment.In order to ensure the homogeneity of the compared groups, only the patients who underwent transhiatal extended gastrectomy (111 patients) were included in the study material, In all patients, in addition to D2 lymphodissection, dissection of the lower paraesophageal lymph nodes was also performed.Neoadjuvant chemotherapy was administered to 9 patients in the unresectable locoregional stage. Although the effect was observed in 7 patients, 6 patients agreed to radical surgery (66.7%).

Adjuvant chemotherapy (mainly Cisplatin, 5-fluorouracil-based) was administered to 82 patients. 38 patients refused adjuvant chemotherapy. A comparative analysis of survival rates showed that the 5-year survival rate of patients treated without adjuvant chemotherapy was 34.8%, and that of patients treated with adjuvant therapy was 45.4%.

Thus, we have found that adjuvant chemotherapy after radical surgery in cases of Siewert II adenocarcinoma of the esophagogastric junction is able to increase the 5-year survival rate by more than 10% on average. The difference between these survival rates was statistically significant. In our opinion, the current scientific research can achieve reliable results because of the same age and sex composition of the compared groups, the same volume of surgery, and the fact that the surgery was performed by the same surgical team.

The difference between these survival rates was statistically significant. Thus, based on our results, we can say with confidence that adjuvant chemotherapy for Siewert type II adenocarcinoma of the esophagogastric junction increases the effectiveness of radical surgery. ($p < 0.05$).

CONCLUSIONS

1.Siewert type II EGJ is associated with intestinal metaplasia of the gastric mucosa and H. pylori infection in the stomach in fewer cases compared with gastric cancer (respectively, 68.7% vs 40.7%, $p<0.05$, 56.3% vs 29.6%, $p<0.05$). Besides, Siewert II type EGJ has a G3-G4 gradation in more cases than gastric cancer (respectively, 82.8% vs 73.0%, $p<0.05$). Significant differences in these parameters are indirect manifestations of the fact that Siewert type II EGJ is a unique oncological unit [10,11].

2. In Siewert II type EGJ, the lower mediastinal (zone 110) lymph nodes are exposed to metastatic damage only in a few patients (3.3% in our results). Metastatic lesions of these lymph nodes are detected rarely and exclusively in N3 stage tumors ($p < 0.001$) which indirectly confirms their location above the antegrade lymph flow [7,8].

3.Transhiatal extended gastrectomy in Siewert type II EGJ is able to ensure R0 resection in 97.3% of cases ($p < 0.001$). In other words, in Siewert type II EGJ, transhiatal extended gastrectomy provided an adequate distance from the tumor to the proximal and dissection of the 110th lymph node with rare metastatic damage may justify the unnecessity for radical transthoracic surgery [1,12,14].

4.Multiorgan resection with extended lymphodissection in T4b stage Siewert type II EGJ does not increase postoperative aggravation and mortality but provides a satisfactory (46.4%) 5-year survival rate (48.1% in T2-T3 stage cancer $p>0.05$) [3,6,15].

5.Adjuvant chemotherapy is able to significantly increase the 5-year survival rate in the T2-T4b stage Siewert type II EGJ, (34.4% vs. 45.4%, $p < 0.05$) [4,9].

PRACTICAL RECOMMENDATIONS

1. It is advisable to accurately identify the type of EGJ according to the Siewert classification, and thus to use the data obtained from CT examination as a basis for choosing an appropriate approach prior to radical surgery. In determining the type of EGJ according to the Siewert classification, CT examination has an accuracy of up to 97.6% and in this regard, it is more accurate than esophagogastroscopy ($p<0.01$).
2. Since large lymph nodes suggesting metastatic damage during the preoperative examination of the lower mediastinal (zone 110) is an indirect manifestation of the highest stage of category N, it may be more effective to initiate treatment with neoadjuvant chemotherapy in these cases;
3. Transhiatal extended gastrectomy in Siewert type II EGJ performed with a high frequency of R0 resection (97.3%) and satisfactory dissection of the lower mediastinal lymph nodes is accompanied by minimal postoperative complication and mortality (1.8%). Therefore, it can be considered as an optimal surgery in terms of ensuring that elderly, weakened persons and patients having concomitant diseases benefit from radical surgery;
4. Adjuvant chemotherapy is required after transhiatal enlarged gastrectomy in the T2-T4b stage Siewert type II EGJ;
5. Due to locoregional reasons – the infiltrative spread of the tumor to adjacent organs, and because the use of neoadjuvant chemotherapy provides an opportunity for two out of three patients to receive radical surgery, the application of the mentioned treatment for patients who could not undergo radical surgery, due to enlargement of regional lymph nodes in the form of conglomerates, is expedient and necessary.

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ABBREVIATIONS

USA – United States of America
AJCC – American Joint Committee on Cancer
AMU – Azerbaijan Medical University
EGJ – esophagogastric junction
IGCA – International Gastric Cancer Association
ISDE – International Society for Diseases of the Esophagus
UICC – Union for International Cancer Control
JRSGC – Japanese Research Society for Gastric Cancer
CT – computed tomography
CNS - central nervous system

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