

## **SURGICAL PALLIATIVE AND SYMPTOMATIC TREATMENT OF REGIONAL CANCER OF THE CARDIOESOPHAGEAL JUNCTION**

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**Annotation:** The article deals with the issues regarding the optimization of surgical treatment strategies in regional and metastatic cancer of the cardioesophageal junction which result in elimination of gastric fistulas. Short- and long-term effects of 238 surgeries between 1990 and 2010 have been studied. The benefits of surgical and endoscopic esophageal stenting over gastrostomy have been reported. The indication for and esophageal stent placement procedures have been defined. The article concludes that cytoreductive transpleural resection surgeries were not associated with increased post-operative mortality. However, they resulted in prolongation of patient's lives and creating proper conditions for delivering adjuvant chemotherapy.

**The key words:** cancer of the cardioesophageal junction, stenting, cytoreductive palliative resection surgery

**Introduction:** The age of high-tech surgery and targeted chemotherapy has significantly expanded the boundaries of treatment methods for common malignant neoplasms. Today, the tactics of persistent surgical cytoreduction in entire branches of palliative oncosurgery are no longer disputed - in colorectal cancer, kidney cancer, ovarian cancer [2,3]. The arsenal of endoscopic methods aimed at preserving and restoring the quality of life of patients has been expanded [4,5,6]. Our research is devoted to the study of such trends in surgery for common and metastatic juxtacardial cancer.

**Objective of the work:** To develop a modern tactic of palliative and symptomatic surgical treatment of patients with stenotic forms of widespread cancer of the cardioesophageal junction, freeing patients from carriage of gastrostomy tubes.

**Material and methods:** By juxtacardial we mean gastroesophageal glandular and esophageal squamous cell carcinomas with the epicenter in the projection of the Z-line of the esophagogastric junction or 5 cm from it on both sides of the diaphragm, which have much in common in surgical treatment approaches. From 2017 to 2024, 722 such patients were under observation in the thoracoabdominal department of RSOARSC, of which 226 (31.3%) had stage IV of the disease. Until 2020, only typical resections of

the cardia and lower thoracic esophagus through right-sided pleural access were performed as radical operations. In case of widespread cancer, following classical guidelines, 50 gastrostomies were formed during this period, which constituted the control group of the study. After 1996, surgical tactics were modernized, using extended D3 and extended-combined resections through the right and left transpleural approaches for radical purposes. Having fundamentally abandoned gastrostomy, 135 stenting and 53 palliative resections of advanced juxtacardiac carcinomas were performed at this time. These cases were included in the 1st main and 2nd main study groups.

### List 1 General characteristics of patients with advanced juxtacardial cancer

Parameters	Gastrosto my. Control group (n=50)	Stenting. Main group 1 (n=135)	Palliative resections. Main group 2 (n=53)
Middle age	59,9±8,1	62,1±9,2	55,5±9,0*
Locally advanced cancer	50,0±6,1%	13,3±2,9%*	45,3±6,8%
Metastatic cancer	50,0±6,1%	86,7±2,9%*	54,7±6,8%
Dysphagia III-IV degree.	62,0±3,1%	96,3±1,2%*	13,2±4,2%*
BMI < 16 kg/m <sup>2</sup>	34,0±6,7%	33,3±4,1%	7,5±3,6%*
Life- threatening complications (bleeding, perforation, anemia)	38,0±6,9%	18,5±3,3%*	34,0± 6,5%
Associated diseases	66,0± 6,7%	66,7± 4,1%	69,8± 6,3%

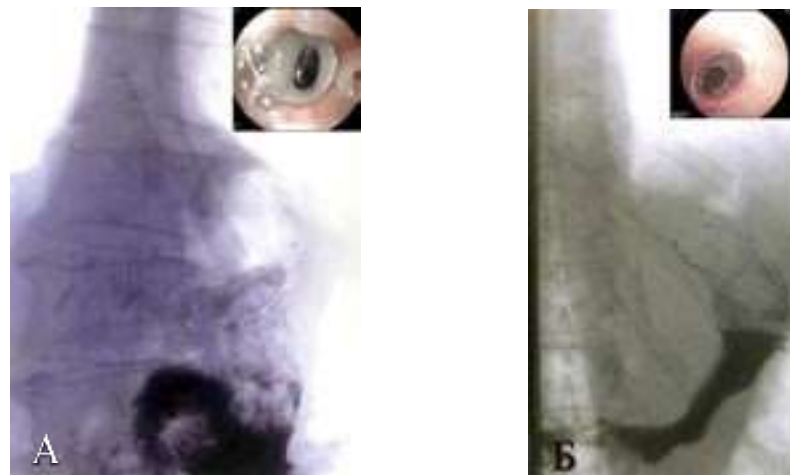
The observation data were distinguished by the predominance of men - 177 (74.4±2.9%) at the average age of 60.2±9.3 years with predominantly gastric adenocarcinoma - 188 (78.7±2.7%) with metastases (71.8±2.9%) and extensive local spread (75.6±2.8%). All patients suffered from dysphagia: in 73.9±2.8% - III-IV degree, which prompted to look for modern methods of its elimination. The leading symptom was exhaustion with BMI < 16 (27.7±2.9%), which retouched other

manifestations of the disease and the severity of concomitant diseases. The group distribution of characteristics is presented in Table 1, while the indicators of stoma and stented patients were uniform in terms of initial parameters. Reliable differences concerned candidates for palliative resection. The criteria for their operability were distinguished by a certain strictness: relatively young patients were selected, not exhausted by dysphagia and exhaustion due to terminal dissemination. The methods of gastrostomy were generally accepted: 26 of them were formed according to the Witzel method, 24 - according to Toprover.

Of the 135 stentings, 120 were performed using rigid prostheses of our own production made of polyethylene, approved for use in the food and medical industries (Fig. 1A). The manufacturing technology is simple and inexpensive. The prosthesis with a diameter of 1 cm was held in the tumor due to the ribbed outer surface, the socket in its proximal part and the locking ring installed on the thread in the distal part after gastrotomy. An antireflux cuff is also mounted here. The kit includes a guidewire, through which a bougie equipped with an endoprosthesis is delivered into the lumen of the tumor. In case of a complex internal relief of the tumor, a preliminary trial introduction of the guidewire was performed under X-ray control, which was never accompanied by iatrogenic perforations. In 18 cases, we were unable to perform preliminary intubation of the stomach with a guidewire and successfully solved this problem during the operation using manual control through the lumen of the stomach after gastrotomy.

In 14 gastroesophageal cancers with total damage to the gastric wall, gastrotomy was impossible. The prosthesis was installed without any particular difficulties and was not equipped with either a locking ring or an antireflux cuff. The critical moment in these cases was considered to be the correct assessment of the density of fixation of the prosthesis in the tumor, the only thing that prevents it from shifting into the esophagus.

Having gained positive experience in 103 open surgeries, in 17 favorable cases, when the anterior wall of the stomach was almost intact, accessible for instrumental palpation and allowed monitoring the endogastric manipulators, we used laparoscopic control. For this, the camera was installed paraumbilically, and the manipulation laparoport was installed under the xiphoid process. Through it, the stent was identified, retained in the stomach and fixation was assessed. Also, since 2008, we endoscopically installed 15 self-expanding covered stents of Korean manufacture under direct X-ray television control (Fig. 1B).

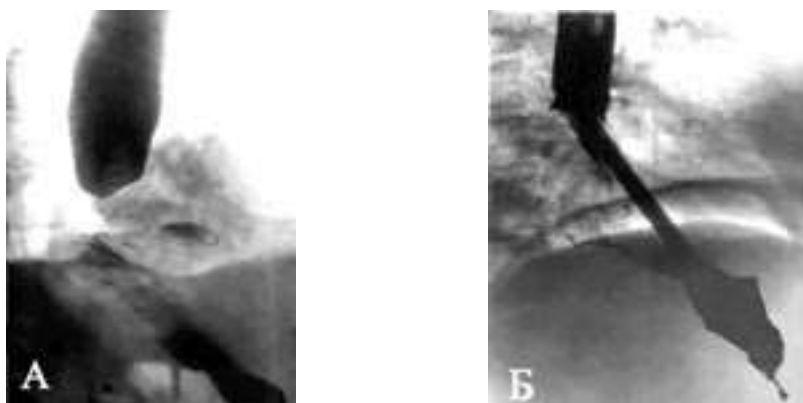


**Fig. 1. Radiographs and endophotos of rigid (A) and self-expanding (B) stents**

Among 53 palliative interventions, there were 19 proximal resections and 34 gastrectomies: in the extended version D 2.3-36 ( $67.9 \pm 6.4\%$ ) cases and in the combined version – 23 ( $43.4 \pm 6.8\%$ ) with splenectomy (17), subtotal pancreas resection (6), liver resection (3), hemicolectomy (3), pericardial resection, diaphragm and adrenalectomy (3). In 3 cases ( $5.7 \pm 3.2\%$ ) after extensive resections, one-stage coloesophagoplasty was performed. Thus, every second palliative resection differs from the standard.

**Results and discussion:** The expected low life expectancy ( $3.4 \pm 0.2$  months) after gastrostomy was accompanied by an unexpectedly high mortality ( $12.0 \pm 3.6\%$ ) and complication rate ( $40.0 \pm 6.9\%$ ), among which were predominantly purulent (necrosis of the stoma, maceration of the skin, abscess formation). The main reason for this was the difficulty of ostomy of the paracancerous inflamed stomach, fixed by an extensive tumor. In light of the control results, the safety of gastrostomies in widespread cardioesophageal cancer seemed to us exaggerated.

When installing 135 stents in the cardioesophageal zone transition revealed 17 ( $12.6 \pm 2.9\%$ ) complications with 3 ( $2.2 \pm 1.3\%$ ) fatal outcomes. The immediate results looked preferable to the control ( $p < 0.05$ ), while the life expectancy of patients did not change significantly –  $4.6 \pm 0.2$  months. The open method was used in difficult situations: with extended stenosis (22); complex internal tumor relief (24); with complete persistent strictures (15), tolerant to electrosurgical recanalization (3); in emergencies (16); in combination with combined gastroenterostomies in pylorobulbar stenosis (2); after previously undergone laparotomies (18); and also in cases of recurrent cancer in the anastomoses (3) (Fig. 2).



**Fig. 2. A. Condition after subtotal proximal gastrectomy with resection of the thoracic esophagus, recurrence in the anastomosis area, complete dysphagia.**

**Б. Condition after endoprosthetics**

After 103 laparotomic stentings, there were 13 complications (12.6±3.3%), including 2 (1.9±1.3%) fatal. Specific complications of rigid stenting included 2 (1.9±1.3%) cases of linear rupture of circular short tumor strictures obtained with excessively violent introduction of prostheses, which ultimately hermetically covered the perforation zones, as well as migration of 2 (1.9±1.3%) stents: one - into the esophagus, brought down by restenting; the second - into the stomach, removed, the stomach was ostomy. There were 2 (1.9±1.3%) fatal bleedings. Moreover, in one of them the source was a tumor, in the other - a duodenal ulcer, synchronous with widespread gastric cancer.

For 17 laparoscopically supported prosthetics, cases with simple execution technique were selected. Complications occurred twice (11.8±7.8%) with one (5.9±5.7%) fatal outcome from pulmonary embolism. Conversion to laparotomy was required once - with a persistent stricture that was not amenable to bougienage. In the absence of complications, patients began to eat liquid mixtures, cereals, purees, minced meat by the end of the first or second day. There were no dietary restrictions at all for 15 patients who were given self-expanding nitinol prostheses using generally accepted methods with 2 (13.3±8.8%) complications in the form of pneumonia (1) and stent migration (1), eliminated by endoscopic repositioning. In 8 cases, sessions of preliminary electro-surgical recanalization were required to achieve a tumor channel diameter of 0.9 cm.

After 53 palliative transpleural resections, there were 13 (24.5±5.9%) complications and 1 (1.9±1.9%) death from depressurization of the esophageal-small intestinal anastomosis. Pleuropneumonia, edematous forms of postoperative pancreatitis, and a few cases of suppuration of the postoperative wound prevailed. The risk of complications was not associated with either the volume of operations, or with cytoreductive lymph node dissection, or with coloesophagoplasty.

All patients were rehabilitated by the end of 3 weeks after surgery and could begin full-fledged chemotherapy in conditions of complete elimination of the source of dysphagia, bleeding, tumor decay. Cytoreductive resections in peritoneal dissemination limited to one floor of the abdominal cavity (P1), in stage IIIb, with minimal macroscopic residual tumor (R2) had independent therapeutic potential, when they reliably increased the life expectancy of patients to  $17.1 \pm 2.4 - 23.3 \pm 3.3$  months.

**Conclusion:** In a modern specialized hospital, gastrostomy for widespread juxtacardiac cancer is an outdated procedure. It is unsafe and physically and mentally exhausting for patients. A better quality of life and a varied diet are provided by the stenting technique. Stenting is indicated for "impacted" carcinomas, at the end of tumor progression, in elderly patients. In partial dysphagia and recanalized tumor, it is preferable to install a flexible prosthesis under endoscopic control, or a rigid prosthesis using laparoscopic access. In case of complete and complex stricture, or the threat of unclear fixation of a rigid stent, it is installed in an "open" way, which helps to reduce the frequency of complications and mortality in comparison with gastrostomies.

#### LIST OF REFERENCES

1. Aggarwal C. et al. A phase 1, open-label, dose-escalation study of enoblituzumab in combination with pembrolizumab in patients with select solid tumors // *J. Immunother. Cancer.* - 2018. - T. 6. - №. Suppl. 2. - C. 114.
2. Aleksander S. A. et al. The Gene Ontology knowledgebase in 2023 // *Genetics.* - 2023. - T. 224. - №. 1. - C. iyad031.
3. Baj J. et al. Immunological aspects of the tumor microenvironment and epithelial-mesenchymal transition in gastric carcinogenesis // *International journal of molecular sciences.* - 2020. - T. 21. - №. 7. - C. 2544.
4. Chen L. et al. Cancer associated fibroblasts promote renal cancer progression through a TDO/Kyn/AhR dependent signaling pathway // *Frontiers in Oncology.* - 2021. - T. 11. - C. 628821.
5. Chen P., He Y., Zhou C. P47. 13 Galectin-9, A Novel Prognostic Factor in Small Cell Lung Cancer // *Journal of Thoracic Oncology.* - 2021. - T. 16. - №. 3. - C. S498.
6. Chocarro L. et al. Understanding LAG-3 signaling // *International journal of molecular sciences.* - 2021. - T. 22. - №. 10. - C. 5282.
7. Compagno D. et al. Galectins as checkpoints of the immune system in cancers, their clinical relevance, and implication in clinical trials // *Biomolecules.* - 2020. T. 10. - №. 5. - C. 750.
8. Cui J. et al. Pancancer analysis of revealed TDO2 as a biomarker of prognosis and immunotherapy // *Disease Markers.* - 2022. - T. 2022. - C. 1-18.
9. Doroshov D. B. et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors // *Nature reviews Clinical oncology.* - 2021. - T. 18. - №. 6. - C. 345362.

10. Edwards D. R., Handsley M. M., Pennington C. J. The ADAM metalloproteinases// Molecular aspects of medicine. - 2008. - T. 29. - №. 5. - C. 258-289.
11. Elad-Sfadia G. et al. Galectin-3 augments K-Ras activation and triggers a Ras signal that attenuates ERK but not phosphoinositide 3-kinase activity // Journal of Biological Chemistry. - 2004. - T. 279. - №. 33. - C. 34922-34930.
12. Gooz M. ADAM-17: the enzyme that does it all // Critical reviews in biochemistry and molecular biology. - 2010. - T. 45. - №. 2. - C. 146-169.
13. Gu L. et al. PD-L1 and gastric cancer prognosis: A systematic review and metaanalysis // PloS one. - 2017. - T. 12. - №. 8. - C. e0182692.
14. He W. et al. CD155/TIGIT signaling regulates CD8+ T-cell metabolism and promotes tumor progression in human gastric cancer // Cancer research. - 2017. - T. 77. - №. 22. - C. 6375-6388.
15. Henson D. E. et al. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type // Archives of pathology & laboratory medicine. - 2004. - T. 128. - №. 7. - C. 765770.
16. Heusschen R., Griffioen A. W., Thijssen V. L. Galectin-9 in tumor biology: a jack of multiple trades // Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. - 2013. - T. 1836. - №. 1. - C. 177-185.
17. Huang D. W. et al. CD155 expression and its correlation with clinicopathologic characteristics, angiogenesis, and prognosis in human cholangiocarcinoma // OncoTargets and therapy. - 2017. - C. 3817-3825.
18. Iguchi-Manaka A. et al. Increased soluble CD155 in the serum of cancer patients // PloS one. - 2016. - T. 11. - №. 4. - C. e0152982.
19. Joossens J. V. et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group // International journal of epidemiology. - 1996. - T. 25. - №. 3. - c. 494-504.
20. Keir M. E. et al. PD-1 and its ligands in tolerance and immunity // Annu. Rev. Immunol. - 2008. - T. 26. - № 1. - C. 677-704.
21. Kim S. J. et al. Fascin expression is related to poor survival in gastric cancer // Pathology international. - 2012. - T. 62. - №. 12. - C. 777-784.
22. Larsson S. C., Bergkvist L., Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study // Cancer Epidemiology Biomarkers & Prevention. - 2006. - T. 15. - №. 10. - C. 1998-2001.
23. Lee B. H. et al. Prognostic value of galectin-9 relates to programmed death-ligand 1 in patients with multiple myeloma // Frontiers in Oncology. - 2021. - T. 11. - C. 669817.

24. Li F. et al. CD4/CD8+ T cells, DC subsets, Foxp3, and IDO expression are predictive indicators of gastric cancer prognosis // *Cancer medicine*. - 2019a. - T. 8. - №. 17. - C. 7330-7344.
25. Li Y. C. et al. Overexpression of an immune checkpoint (CD155) in breast cancer associated with prognostic significance and exhausted tumor-infiltrating lymphocytes: a cohort study // *Journal of immunology research*. - 2020. - T. 2020. - C. 1-9.
26. Li Y. et al. B7-H3 increases the radioresistance of gastric cancer cells through regulating baseline levels of cell autophagy // *American journal of translational research*. - 2019c. - T. 11. - №. 7. - C. 4438-4449.
27. Linsley P. S. et al. Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors // *Immunity*. - 1994. T. 1. - №. 9. - C. 793-801.
28. Liu H. et al. Increased expression of IDO associates with poor postoperative clinical outcome of patients with gastric adenocarcinoma // *Scientific Reports*. -2016. - T. 6. - №.1. - C. 21319.
29. Lordick F. et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up^ // *Annals of Oncology*. - 2022. - T. 33. - №. 10. - C. 1005-1020.
30. Lu S. et al. Expression of indoleamine 2, 3-dioxygenase 1 (IDO1) and tryptophanyl-tRNA synthetase (WARS) in gastric cancer molecular subtypes // *Applied immunohistochemistry & molecular morphology: AIMM*. - 2020. - T. 28. - №. 5. - C. 360-368.
31. Ma W. et al. Targeting immunotherapy for bladder cancer by using anti-CD3x CD155 bispecific antibody // *Journal of Cancer*. - 2019. - T. 10. - №. 21. - C. 5153-5161.
32. Mai P. L. et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort // *Cancer*. - 2016. - T. 122. - №. 23. - C. 3673-3681.
33. Masciari S. et al. Gastric cancer in individuals with Li-Fraumeni syndrome // *Genetics in Medicine*. - 2011. - T. 13. - №. 7. - C. 651-657.
34. McDermott D. et al. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20) // *Annals of Oncology*. - 2013. - T. 24. - №. 10. - C. 2694-2698.
35. Möller-Hackbarth K. et al. A disintegrin and metalloprotease (ADAM) 10 and ADAM17 are major sheddases of T cell immunoglobulin and mucin domain 3 (Tim-3) // *Journal of Biological Chemistry*. - 2013. - T. 288. - №. 48. - C. 3452934544.



36. Moss M. L. et al. Recent advances in ADAM17 research: a promising target for cancer and inflammation // *Mediators of inflammation*. - 2017. - T. 2017. C. 121.
37. Nakahara S., Raz A. Regulation of cancer-related gene expression by galectin-3 and the molecular mechanism of its nuclear import pathway // *Cancer and Metastasis Reviews*. - 2007. - T. 26. - № 3-4. - C. 605-610.
38. Ochs K. et al. Tryptophan-2, 3-dioxygenase is regulated by prostaglandin E2 in malignant glioma via a positive signaling loop involving prostaglandin E receptor-4 // *Journal of neurochemistry*. - 2016. - T. 136. - №. 6. - C. 1142-1154.
39. Okada K. et al. Reduced galectin-3 expression is an indicator of unfavorable prognosis in gastric cancer // *Anticancer research*. - 2006. - T. 26. - №. 2B. - C. 1369-1376.
40. Parsonnet J. et al. Helicobacter pylori infection in intestinal-and diffuse-type gastric adenocarcinomas // *JNCI: Journal of the National Cancer Institute*. - 1991. T. 83. - №. 9. - C. 640-643.
41. Patel S. P., Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy // *Molecular cancer therapeutics*. - 2015. - T. 14. - №2. 4. - C. 847856.
42. Peyraud F. et al. Targeting tryptophan catabolism in cancer immunotherapy era: challenges and perspectives // *Frontiers in Immunology*. - 2022. - T. 13. - C. 807271.
43. Kuliev A.A., Juraev M.D. и др. // *Turkish Journal of Physiotherapy and Rehabilitation*; 32(3) 2021. C 7242-7245
44. Кулиев А.А., Джураев М.Д. и др. // *Academic research in educational sciences scientific journal* 2021. №2. C 291-307
45. Кулиев А.А., Джураев М.Д. и др. // *Журнал биомедицины и практики*; №2 2021. C 132-138.
46. Kuliev A.A., Juraev M.D. и др. // *The American Journal of Medical Sciences and Pharmaceutical Research* (ISSN – 2689-1026) 2023. C 70-77.