

ON THE QUESTION OF INDICATIONS AND CHOICE OF THE METHOD OF PALLIATIVE SURGERY IN PATIENTS WITH STOMACH CANCER

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Annotation: The article presents the results of palliative surgeries of varying scope performed in 65 patients with stage IV gastric cancer. Indications for palliative surgery were massive gastric bleeding or obstruction of various parts of the stomach. Life expectancy of this category of patients is limited to several months in most cases, less often - 1-2 years. Gastrostomy should be extremely limited and at the same time indications for total gastrectomy should be expanded, which allows eliminating the cause of obstruction and bleeding from the gastric tumor. During gastrectomy, the formation of the esophageal-intestinal anastomosis can be performed using a suturing device (SPTU, EEA). Patients who have undergone surgical interventions of varying scope need to improve their quality of life, which is achieved by relieving the patient of pain, creating the opportunity to eat, improving metabolic processes, preventing rapid weight loss due to periodic intravenous infusions of colloidal and crystalloid solutions (including fresh frozen plasma), maintaining mental status. Improving the quality of life of a large contingent of doomed patients who have undergone various levels of palliative surgical interventions should be considered the most important task of practical health care.

Key words: stage IV gastric cancer, palliative surgery, indications for hysterectomy, body weight, quality of life of patients

Surgical treatment of gastric cancer inevitably faces the problem of medical care for those patients whose tumor is unresectable, allowing only palliative surgical intervention. The question of the advisability of performing palliative surgeries of varying volumes remains unresolved to date, and sometimes even controversial, which is confirmed by the lack of specific indications for performing a particular intervention in a specific situation [3, 4, 6]. According to E. Kotan et al. [5], the frequency of palliative surgeries for gastric cancer of stages IIIA, IIIB, IV is an average of 42.6%, and directly for stage IV - 14.4%. These data confirm a very high percentage of palliative surgeries performed for gastric cancer.

Objective of the work: To clarify the indications for performing palliative surgeries in patients with stage IV gastric cancer and to provide a clinical justification for choosing one or another method of surgical intervention.

Material and methods: We observed 65 patients with gastric cancer who underwent palliative surgery. The patients were aged from 35 to 78 years. There were 47 men and 18 women. Various volumes of surgery were performed: gastrostomy, gastroenterostomy, gastric resection, etc. Along with general clinical, clinical and laboratory studies, body weight was determined in patients before and after surgery, taking into account the change in the Broca index. The quality of life of patients was assessed using the SF-36 Health Status Survey method.

Research results and their discussion: Of the 65 patients we analyzed, the scope of surgical interventions was as follows: gastrostomy, jejunostomy, formation of gastroenteroanastomosis, Bilioth-II gastric resection, gastrectomy, esophagogastrectomy, formation of esophagojejunostomy (table).

The nature of palliative surgery in patients with gastric cancer

Operation	Quantity	
	operations	deceased
Gastrostomy	9	1
Jejunostomy	9	-
Gastroenterostomy	21	1
Esophagojejunal anastomosis	2	-
Gastric resection	10	2
Gastrectomy	14	2
Total	65	6

As can be seen from the table, out of 65 palliative operations, gastrostomy was performed in 9 patients, of whom 1 patient died in the early postoperative period. All gastrostomies were performed using the Witzel method, as the simplest in technical execution. Gastrostomy allows only to some extent to raise the moral state of the patient. The negative aspects of gastrostomy are inherent to jejunostomy to one degree or another. Each of these operations can be called an "operation of despair" or an operation of "mercy". Jejunostomy was performed using the Meidl method in all 9 patients with inoperable cancer of the cardiac part of the stomach.

In inoperable cancer of the distal stomach complicated by obstruction of the pyloroantral zone, surgery with the formation of a bypass anastomosis, in particular, gastroenterostomy, has become widespread in clinical practice. If in the treatment of peptic ulcer disease gastroenterostomy has almost completely lost its practical significance, then in gastric cancer it is used to this day.

Gastroenteroanastomosis in gastric cancer brings relief to the patient in most cases, eliminating congestion in the stomach cavity during obstruction of the pyloric zone and normalizing the motor-evacuation function of this organ. The consequence of this is the cessation of painful vomiting in the patient, an improvement in the general condition, the ability to eat, some temporary stabilization of body weight and an improvement in psychological status.

In the group of palliative surgeries analyzed by us, gastroenterostomy was performed in 21 patients, of whom one patient died in the early postoperative period. In all patients, gastroenterostomy was performed in two variants - anterior and posterior. A simpler variant is the formation of a posterior gastroenteroanastomosis, which does not require the formation of an interintestinal, Brown, anastomosis. It is very difficult to determine the effect of gastroenterostomy on the patient's condition. The desire to recover, the belief in the absolute "radicality" of the operation often make the patient and his relatives somewhat overestimate the true result of the operation. Some patients assess their condition as "good" or "normal" even several weeks, and sometimes days before death. Side effects are usually associated with the normalization of food passage, the disruption of which the patient considered the main symptom of the disease before the operation. Since such an assessment is not so rare, the main factor in assessing the operation - survival - in the case of a palliative operation is usually considered less significant than the general well-being and psychological status of the patient, who does not experience daily distressing symptoms of obstructive obstruction of the pyloroantral part of the stomach. In this regard, judgments about the advisability of performing palliative operations are not always based on any objective criteria, and therefore the benefits of treating this category of patients often seem to be only apparent. Hence the gratitude or dissatisfaction of patients from the attitude towards the operation and everything connected with it, as well as from the expectation of purely individual results [1].

As clinical practice shows, attempts to cure a patient with stomach cancer often prove fruitless. Removal of the stomach tumor itself at any cost is usually associated with the risk of developing severe and dangerous postoperative complications and, thus, reducing the chances of not only a satisfactory existence, but also life. The situation changes significantly when it comes to dealing with complete or almost complete obstruction of the pyloroantral section due to a cancerous tumor. In this situation, any risk of surgery becomes justified. The surgeon must take into account the patient's capabilities before and during the operation and mentally imagine the expected therapeutic effect of the surgical intervention. In this case, the surgeon's medical experience and his skill as an operator are often very important, although the latter often recedes into the background due to the impossibility of performing a radical intervention.

In proximal stomach cancer, the surgeon sometimes has to perform an operation to form a bypass anastomosis between the esophagus and the jejunum (esophagojejunostomy), despite its technical difficulties. This operation uses both intrathoracic (intrapleural) and transperitoneal access in combination with mediastinotomy according to A.G. Savinykh. Great hopes were pinned on such operations: their "undoubted" advantages over classical gastrostomy were proven both in the moral sense for the patient and in terms of immediate and remote results. Subsequent clinical observations confirmed the technical complexity of performing this type of operation, which gives a high mortality rate and a slight extension of the life expectancy of those who underwent the operation. And yet, these operations can be performed according to strict indications, when the patient has distressing symptoms of dysphagia in the presence of a technically unremovable tumor of the cardiac part of the stomach. The formation of such a bypass anastomosis creates confidence in "recovery" in most patients who have undergone the operation.

The technique of forming bypass anastomoses in most cases is complicated, especially in case of large tumors of the proximal stomach and tumor spread to the abdominal esophagus. In such circumstances, the surgeon's technical capabilities often cannot be realized despite his best efforts and he has to retreat. The bottom of the stomach in these conditions is occupied by the tumor and cannot be used for anastomosis, and the small intestine, when thrown over the tumor mass, even with additional mobilization by dissection of the vascular arcades of the jejunum, is stretched, which makes it necessary to abandon the formation of esophagojejunostomy. In this situation, the probability of failure of the anastomosis sutures with subsequent development of purulent peritonitis and other complications is too high. Esophagojejunostomy is formed according to well-known principles. The jejunum loop taken for the anastomosis should be freely pulled to the required level on the esophagus, and only after that a side-to-side anastomosis is formed, and then an inter-intestinal anastomosis is formed. The length of the afferent loop should be at least 30 cm. If the intestine is not pulled to the required level, it is more advantageous to form an esophageal-intestinal anastomosis using the Roux-en-Y method (U-anastomosis). In this case, the distal end of the crossed loop is sutured tightly with a two-row suture, and then an esophageal-intestinal anastomosis is formed using the side-to-side method.

It should be taken into account that many patients soon after the formation of a bypass esophagoenteroanastomosis complain of a continuing feeling of stomach fullness, periodically appearing rotten belching. Despite the restoration of patency from the esophagus to the intestine, gastroenterostomy does not always eliminate the phenomena of stagnation and fermentation in the stomach. Unfortunately, these symptoms do not go away over time, often even intensify, the patient begins to worry, losing faith in the effectiveness of the surgical intervention, and begins to suspect

deception with all the ensuing consequences, which leads to a violation of the trusting contact between the patient and the doctor.

Taking these points into account, we performed total gastrectomy in a number of patients using the SPTU suturing device to reduce the duration of the operation, which allows for the rapid formation of an esophageal-intestinal anastomosis with tantalum staples in the form of a single-row circular suture, after which a second row is applied manually with U-shaped sutures. The operation is completed by forming an interintestinal anastomosis and wide drainage of the abdominal cavity. Although such an operation takes longer than a conventional gastroenterostomy, it saves the patient from bleeding, perforation of a cancerous tumor, completely restores the patency of food through the esophageal-intestinal complex and eliminates the clinical symptoms of stagnation and fermentation [2]. We performed gastrectomy in 14 of 65 patients in the analyzed group of palliative operations and received two deaths directly in the postoperative period from peritonitis. Thus, the overall mortality rate of patients after palliative surgery averaged 6.2%.

The physician preparing for the operation of each patient for gastric cancer faces great difficulties in choosing an objective criterion for assessing the degree of weight loss. Usually, the patient's body weight before the operation, calculated taking into account the Broca index, is taken as a basis. Of course, this indicator depends on the duration of the disease before the operation, the severity of complications (blood loss, organic pyloric stenosis of tumor etiology, cardiac obstruction, etc.), the degree of intoxication and other factors, but there is no other criterion typical for a given patient. In addition, it should be noted that during the operation and the immediate postoperative period, patients noticeably lose weight. According to our data, the average weight loss in patients who underwent palliative operations, including gastrectomies and esophagogastrectomies, already at 3-6 months was $23.3 \pm 1.4\%$, which corresponds to a body weight deficit of 16.2 ± 1.1 kg. Body weight deficit after surgery from 6 to 10 kg was noted in 23 patients, from 11 to 20 kg – in 21 patients, more than 20 kg – in 13 patients. These data confirm the significant frequency and severity of weight loss in patients who underwent palliative surgery.

The causes of weight loss in patients who have undergone palliative surgeries of various volumes have not yet been established. The literature contains indications of the role of interstitial metabolic disorders in the body due to impaired intracellular protein synthesis caused by deficiency and imbalance of amino acids.

In our opinion, persistent and pronounced weight loss depends on many factors, including the following: 1) insufficient caloric content of food, especially with a decrease in its daily volume;

2) insufficient absorption of food (impaired digestion, decreased absorption, impaired motor-evacuation function of the intestine;

3) development of severe pathological syndromes of the operated stomach (esophagitis, dumping syndrome, etc.), limiting food intake due to pain, dysphagia, diarrhea, flatulence, etc. This ultimately leads to food intake disease (dietophobia), constant malnutrition of patients, further weight loss, up to the development of exhaustion syndrome. All of the above creates a complex clinical symptom complex in each patient, which ultimately forms the clinical appearance of this category of patients with a low quality of life (87.3 ± 1.8 points according to the SF-36 system). Taking into account the above data, the main goal of palliative care for patients who have undergone surgery is to improve their quality of life, which is achieved by relieving the patient of pain, creating the opportunity to eat and normalize sleep, eliminating debilitating constipation or diarrhea, and improving metabolic processes in order to prevent weight loss. This category of patients requires periodic hospitalization in a surgical or oncology department for the purpose of intravenous administration of colloidal and crystalloid solutions, components of preserved blood.

It should be noted that the life expectancy of patients who have undergone such palliative surgeries as gastroenterostomy and gastrectomy depends on the extent of the tumor process, i.e. on the stage of the disease. Since all palliative surgeries are performed mainly at stage IV, less often at stage IIIB, the life expectancy of patients after surgery is measured in weeks and months, and very rarely more than 1 year.

Thus, Yu.E. Berezov, when studying the life expectancy of patients with stomach cancer who underwent gastroenterostomy, obtained the following data [1]: 32 (12.1%) people died in hospital, 62 (23.5%) lived less than 3 months, 76 (28.8%) from 3 to 6 months, 25 (9.5%) from 6 to 9 months, 22 (8.3%) from 9 to 12 months, 7 (2.6%) from 12 to 15 months, 5 (1.9%) from 15 to 18 months, 3 (1.1%) from 18 to 24 months, 1 (0.4%) for 3 years 4 months, and the fate of 31 (11.8%) patients was not traced. These data allow us to ask the question: does gastroenteroanastomosis prolong the life of patients? The answer to this question cannot be statistically processed, but it seems that it should be answered in the affirmative, since some patients (1.7% of those operated on) live for 1.5–2 years, and in addition, this operation has allowed many to eliminate the incredibly painful symptoms of obstruction of the pyloroantral part of the stomach, which is very significant.

Remote consequences of palliative gastrectomy for gastric cancer are extremely insufficiently covered in the modern literature. These data are usually presented together with the results of radical operations. Remote consequences of palliative gastrectomy and esophagogastrectomy in patients with gastric cancer are quite convincingly presented in the work of C. Kotan et al. [5]. The authors conducted a retrospective analysis of the consequences of palliative gastrectomy and esophagogastrectomy in 83 patients (48 men and 35 women), whose average age was 54.6 ± 11.4 years (age from 28 to 80 years). There were 20 patients in stage III A, 35 in

stage III B and 28 in stage IV. The frequency of palliative gastrectomy and esophagogastrectomy averaged 42.6% with a total of 195 patients undergoing all analyzed operations for gastric cancer. The number of patients with stage IV gastric cancer was 14.4%. Of the 83 patients, 8 (9.6%) died in the postoperative period; the causes of death were suture failure (3 patients), myocardial infarction (1 patient), and sepsis (4 patients). The average life expectancy of all surviving patients after surgery was 12.8 ± 0.8 months, at stage III A – 18.16 ± 2.04 , at stage III B – 13.37 ± 0.73 , and at stage IV – 7.51 ± 0.97 months.

A special section is made up of bypass anastomoses in gastric stump cancer. The severity of the clinical picture is determined by the involvement of not only the gastric stump and adjacent organs in the tumor infiltrate, but also the jejunum and transverse colon, as well as the biliary tract. Surgical assistance in this situation is often minimal, and sometimes simply impossible. In most cases, a gastric stump tumor is unresectable, causing various types of obstruction: esophageal, gastric, small intestinal, biliary tract. All this forces the surgeon to resort to palliative surgery, despite its extremely low efficiency. Nevertheless, such a forced operation allows some patients to significantly alleviate their condition in the last months of their lives, some of them manage to prolong the time approaching death, some of them temporarily manage to create the illusion of well-being and even "recovery". Before this, many hours of intense surgical work recede into the background against the background of understanding the inevitability of a fatal outcome, as well as taking into account the possibility of developing severe postoperative complications with a high percentage of mortality in the early stages after surgery.

In case of resectable cancer of the gastric stump with metastases, it should be considered appropriate to perform palliative extirpation of the gastric stump with the imposition of an esophageal-intestinal anastomosis using the SPTU or EEA suturing apparatus instead of forming a bypass esophageal-intestinal anastomosis.

Among palliative surgeries, palliative gastric resections also occupy a large place. At the current stage of development of oncology and surgery, gastric resection (distal or proximal) as a radical operation for gastric cancer should not be performed in the generally accepted classical version and should be replaced by only one alternative surgical intervention - standard or combined gastrectomy in combination with lymph node dissection in the volume of D2 and D3. In this regard, the concept of "gastric resection for cancer" should mean performing the operation only as a half-measure, i.e. palliative intervention. The concept of "palliative resection" should be retained only in those cases when the operation for a resectable tumor due to the presence of undetachable metastases or under forced conditions (bleeding from the tumor, the impossibility of technically completely removing the tumor, cancerous ascites, the

impossibility of suturing the site of cancer perforation in elderly people) is performed deliberately non-radically.

In conclusion, it should be noted that, despite all the pessimism of the data presented, palliative surgeries for stomach cancer are still widely used, often making the last days of life of doomed patients easier. This justifies further searches for a solution to the “ageless” global problem of cancer in medical practice.

Conclusion. 1. Palliative surgical interventions in patients with stage IV gastric cancer should be considered justified, as this allows for an extension of their lifespan by several months, less often by 1-2 years. 2. At the current stage of development of surgery and oncology, the number of gastrostomies and jejunostomies performed should be extremely limited by expanding the indications for palliative total gastrectomy.

1. LIST OF REFERENCES

2. 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.
3. Aleksander S. A. et al. The Gene Ontology knowledgebase in 2023 // Genetics. - 2023. - T. 224. - №. 1. - C. iyad031.
4. 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.
5. 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.
6. 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.
7. Chocarro L. et al. Understanding LAG-3 signaling // International journal of molecular sciences. - 2021. - T. 22. - №. 10. - C. 5282.
8. 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.
9. Cui J. et al. Pancancer analysis of revealed TDO2 as a biomarker of prognosis and immunotherapy // Disease Markers. - 2022. - T. 2022. - C. 1-18.
10. Doroshow 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.
11. Edwards D. R., Handsley M. M., Pennington C. J. The ADAM metalloproteinases // Molecular aspects of medicine. - 2008. - T. 29. - №. 5. - C. 258-289.

12. 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.
13. Gooz M. ADAM-17: the enzyme that does it all // *Critical reviews in biochemistry and molecular biology*. - 2010. - T. 45. - №. 2. - C. 146-169.
14. Gu L. et al. PD-L1 and gastric cancer prognosis: A systematic review and metaanalysis // *PloS one*. - 2017. - T. 12. - №. 8. - C. e0182692.
15. 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.
16. 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.
17. 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.
18. 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.
19. Iguchi-Manaka A. et al. Increased soluble CD155 in the serum of cancer patients // *PloS one*. - 2016. - T. 11. - №. 4. - C. e0152982.
20. 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.
21. Keir M. E. et al. PD-1 and its ligands in tolerance and immunity // *Annu. Rev. Immunol.* - 2008. - T. 26. - №. 1. - C. 677-704.
22. Kim S. J. et al. Fascin expression is related to poor survival in gastric cancer // *Pathology international*. - 2012. - T. 62. - №. 12. - C. 777-784.
23. 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.
24. 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.
25. 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.

- 26.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.
- 27.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.
- 28.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.
- 29.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.
- 30.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.
- 31.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.
- 32.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.
- 33.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.
- 34.Masciari S. et al. Gastric cancer in individuals with Li-Fraumeni syndrome // Genetics in Medicine. - 2011. - T. 13. - №. 7. - C. 651-657.
- 35.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.
- 36.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.
- 37.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.

38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. Peyraud F. et al. Targeting tryptophan catabolism in cancer immunotherapy era: challenges and perspectives // *Frontiers in Immunology*. - 2022. - T. 13. - C. 807271.
44. Kuliev A.A., Juraev M.D. и др. // *Turkish Journal of Physiotherapy and Rehabilitation*; 32(3) 2021. C 7242-7245
45. Кулиев А.А., Джураев М.Д. и др. // *Academic research in educational sciences scientific journal* 2021. №2. C 291-307
46. Кулиев А.А., Джураев М.Д. и др. // *Журнал биомедицины и практики*; №2 2021. C 132-138.
47. Kuliev A.A., Juraev M.D. и др. // *The American Journal of Medical Sciences and Pharmaceutical Research* (ISSN – 2689-1026) 2023. C 70-77.