PROSPECTS FOR NEOADJUVANT TREATMENT OF AMPULLARY CANCER

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Abstract. Objective: to study the possibilities of preoperative radiation therapy in a radical treatment regimen for glandular ampullary cancer.

Materials and methods. In 2001-2019, 21 cases of pancreatic-biliary type of ampullary cancer underwent radical treatment, including preoperative RT, extended GPDR and adjuvant chemotherapy according to indications (experimental group), 48 cases of pancreatic-biliary type of ampullary cancer underwent expanded GPDR and adjuvant chemotherapy according to indications (control group), and 43 cases of intestinal type of ampullary cancer underwent extended GPDR and adjuvant chemotherapy according to indications.

Results. Radiation therapy caused radiation injuries in 28.6% of patients: grade 1 erythema (19.1%), grade 1 leukopenia (4.75%), and grade 2 leukopenia (4.75%). Postoperative complications, mortality of the experimental group and the control group, respectively, amounted to 28.6% and 50.0% ($p = 0.09$) and 4.8% and 6.3% ($p = 0.8$). The overall 5-year survival rate, the average life expectancy of the experimental group and the control group, respectively, were 50.7% and 9.8% ($p = 0.01$) and 74.8 ± 12.58 months and 21.7 ± 6.11 months ($p = 0.0008$). The overall 5-year survival rate, the average life expectancy of the group with intestinal ampullary cancer, were 61.3% and 60.5 ± 9.15 months, respectively. Relapse-free survival of patients with glandular ampullary cancer ($n = 112$) who received treatment according to the radical regimen was: 1-year - 77.8%, 3-year - 51.0%, 5-year - 35.2%, average life expectancy - 44.7 ± 5.44 months

Conclusion. Radiation injuries were stopped by conservative measures and did not increase the duration of the preoperative period. Preoperative RT in the radical treatment regimen for pancreatic-biliary type of ampullary cancer neither changed the nature nor increased the incidence of postoperative complications. Combined treatment significantly improved long-term survival in cases with pancreatic-biliary type of ampullary cancer.

Keywords: ampullary cancer, pancreatic-biliary type, preoperative radiation therapy.

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Introduction

Treatment of cancer of the ampulla of Vater is one of the most complex and yet unresolved problems in oncology. Many tactical and technical issues have remained controversial and far from being addressed.

Currently, the range radical surgical techniques is represented by transduodenal papillectomy and pancreatoduodenal resection (PDR). The indications for transduodenal papillectomy are strictly limited. This range of surgical aid is an alternative in the surgeon's arsenal for patients with severe concomitant pathology, which excludes the use of PDR.

The surgical standard for treatment of ampullary cancer remains PDR with lymphadenectomy.

Postoperative complications account for 22-67%, mortality – 0-9% [1, 2, 3]. Overall survival in observations where the R0 operation was performed: median - 30.1-113 months, 1-year - 75-86.7%, 3-year - 57.3-69.4%, 5-year - 20-88% [4, 5, 6, 7, 8].

To improve long-term results, radical surgery should be integrated into multimodal treatment.

Currently, the data on the effectiveness of the use of adjuvant therapy in the radical regimen for the treatment of ampullary cancer are contradictory. A number of fairly large studies have shown that adjuvant therapy did not improve long-term treatment results. In particular, clinical studies of ESPAC-1 (1997) and EORTC (1999) of pancreatic head cancer and

periampullary cancer did not reveal the effectiveness of adjuvant chemoradiation therapy (CRT) [9, 10]. As a result, the role of CRT in the radical treatment of pancreatic head cancer requires clarification. I. Nassour et al. (2018) noted that in 2004-2013 the treatment of pancreatic head cancer made a shift from adjuvant chemotherapy to chemotherapy (CT), which increased from 9% to 32%. However, adjuvant chemotherapy in periampullary cancer in the ESPAC-3 study (2012), and in ampullary cancer in the ESPAC-3 study (v2, 2016) did not increase life expectancy [12, 13]. Subsequently, Z. Jin et al. (2018), M. Al-Jumayli et al. (2019), B.L. Ecker et al. (2019) did not find a significant increase in long-term survival of patients with ampullary cancer receiving adjuvant treatment.

According to other studies, adjuvant therapy is a promising direction in the combination treatment of ampullary cancer. A meta-analysis of ten retrospective studies, including 3361 observations, showed that adjuvant chemoradiotherapy was associated with a lower risk of death (HR = 0.75; P = 0.001) compared to surgery alone [17]. Analysis of a large sample of NCDB (National Cancer Database) showed that adjuvant chemotherapy significantly increased life expectancy in the group with the T3/T4 index, and adjuvant chemotherapy significantly increased life expectancy in the group with metastatic lymph node lesions [11].

Thus, there are still no randomized controlled trials proving the effectiveness of adjuvant chemotherapy and radiation therapy (RT) for ampullary cancer. Until now, neither the national clinical

guidelines, nor the recommendations of RUSSCO, ESMO, NCCN provide indications and modes of adjuvant chemotherapy in the program of radical treatment of ampullary cancer.

Randomized controlled trials on the neoadjuvant treatment of ampullary cancer are also absent. There is no definitive consensus recommendation for the use of neoadjuvant chemotherapy and radiotherapy for ampullary cancer; in general, treatment is individualized and/or based on regional inpatient protocols.

In conclusion, the issue of neoadjuvant treatment of ampullary cancer remains open. The issue of adjuvant treatment of ampullary cancer has not yet been closed (there are no indications and regimens for adjuvant chemotherapy), and morphological heterogeneity of ampullary cancer determines a large spread in long-term survival rates (5-year from 20% to 88%), which requires the study of prognostic factors, considering the latter, and the development of radical treatment regimens.

Objective: to study the possibilities of preoperative radiation therapy in a radical treatment regimen for glandular ampullary cancer.

Materials and methods

In 2001-2019, 116 patients with glandular ampullary cancer received treatment in the Irkutsk Regional Oncological Dispensary. Of these, 63 (54.3%) were men and 53 (45.7%) - women. Most of the patients were aged 51-70 years (86 - 74.1%); the average age was 59.1 ± 0.83 years (Table 1).

Table 1

Grouping by sex and age			
age	sex		total
	men	women	
30-40	2 (1.7%)	-	2 (1.7%)
41-50	10 (8.6%)	7 (6.0%)	17 (14.7%)
51-60	27 (23.3%)	17 (14.7%)	44 (37.9%)
61-70	21 (18.1%)	21 (18.1%)	42 (36.2%)
over 70	3 (2.6%)	8 (6.9%)	11 (9.5%)
	63 (54.3%)	53 (45.7%)	116 (100%)
total	116 (100%)		

Ninety-one (78.4%) of 116 patients with ampullary cancer were admitted to the dispensary with obstructive jaundice. At the pre-specialized stage, the following bile diversion techniques were performed: cholecystostomy by projection access - 12 (13.2%), laparoscopic cholecystostomy - 15 (16.5%), endoscopic stenting of extrahepatic bile ducts - 44 (48.3%), external drainage of the common bile duct - 7 (7.7%), formation of biliodigestive anastomoses - 4

(4.4%), cholecystostomy under ultrasound navigation - 1 (1.1%), and endoscopic papillosphincterotomy - 8 (8.8%) cases.

At the diagnostic stage, pancreatobiliary type of cancer was found in 71 (61.2%) cases, and intestinal type of cancer in 45 (38.8%) cases.

Grouping of the patients by morphology and stage of the tumor process is shown in Table 2.

Table 2

Grouping of the patients by morphology and stage of the tumor process			
signs	pancreato-biliary type	intestinal type	total
1. stage of the tumor process			
- IA	9 (12.7%)	8 (17.8%)	17 (14.7%)
- IB	10 (14.1%)	10 (22.2%)	20 (17.2%)
- IIA	12 (16.9%)	6 (13.3%)	18 (15.5%)
- IIB	17 (23.9%)	6 (13.3%)	23 (19.8%)
- III	2 (2.8%)	6 (13.3%)	8 (6.9%)
- IV	21 (29.6%)	9 (20.0%)	30 (25.9%)
total	71 (100%)	45 (100%)	116 (100%)
2. tumor differentiation degree			
- severe	5 (7.0%)	22 (48.9%)	27 (23.3%)
- moderate	53 (74.7%)	17 (37.8%)	70 (60.3%)
- low	13 (18.3%)	6 (13.3%)	19 (16.4%)
total	71 (100%)	45 (100%)	116 (100%)

Stage II of the tumor process (40.8%) and a moderate degree of tumor differentiation (74.7%) prevailed in the pancreatic-biliary type of ampullary cancer. In the intestinal type, stage I of the tumor process (40.0%) and severe tumor differentiation (48.9%) prevailed.

In the structure of ampullary cancer, stage I was in 31.9% of cases, stage II - 35.3%, stage III - 6.9%, and stage IV - 25.9%. Severe tumor differentiation was found in 23.3% of cases, moderate - in 60.3% and low - in 16.4%.

Sixty-nine of 71 cases of pancreatic-biliary type of ampullary cancer received radical treatment; in 2 cases during the operation, metastatic lesions of the liver and carcinomatosis of the abdominal cavity were detected. Forty-three of 45 cases of intestinal ampullary cancer received radical treatment; in 2 cases during the operation, metastatic lesions of the liver and carcinomatosis of the abdominal cavity were detected.

In 21 cases of the pancreatic-biliary type, treatment was started with remote RT (main group), in 48 (control group) - with radical surgery.

Remote RT was started 4 weeks after biliary decompression. Topometry was performed on a multispiral computed tomograph. For better visualization of the tumor and a landmark, X-ray contrast marks were applied, and the introduction of a X-ray contrast agent was also used. Computed tomograms were performed with an interval of 2.5-5 mm, with the scanning level from the upper edge of the liver Th10-11 to L3-4. The second stage was the contouring of the scans obtained as a result of topometry. Planning and dosimetric calculations were performed on a 3-dimensional planning system "Eclipse" (3D) with the exclusion of critical organs (kidney, spinal cord, liver, spleen, small intestine) from the irradiation zone. RT was performed using the classical mode of fractionation ROD-2Gy 5 times a week to SOD-50Gy for 5 weeks.

In 112 (96.5%) cases, a radical volume of the operative manual was completed (Table 3). This group included 21 observations, where treatment was started with remote RT and 91 observations, where treatment was started with radical surgery.

Table 3

Grouping of patients by the extent of surgical aid	
extent of surgical intervention	number
extended gastropancreatoduodenal resection	91 (78.4%)
+ right hepatic artery resection	1 (0.9%)
total	92 (79.3%)
extended gastropancreatoduodenal resection with mesenteric-portal venous segment resection	12 (10.3%)
+ right hepatic artery resection	1 (0.9%)
total	13 (11.2%)
total pancreatoduodenal ectomy	5 (4.3%)
transduodenal papillectomy	2 (1.7%)
explorative laparotomy	3 (2.6%)
hepaticojejunostomy, gastrojejunostomy	1 (0.9%)
total	116 (100%)

Ninety-one (78.4%) cases underwent extended gastropancreatoduodenal resection (GPDR), 12 (10.3%) cases - extended GPDR with resection of the mesenteric-portal venous segment (MPVS), 1 (0.9%) - expanded GPDR with resection of the right hepatic artery, 1 (0.9%) - extended GPDR with resection of the MPVS and the right hepatic artery, 5 (4.3%) - total duodenopancreatotomy, 2 (1.7%) - transduodenal

papillectomy, in 3 (2.6%) - trial laparotomy, and 1 (0.9%) - hepaticojejunostomy, gastrojejunostomy.

Currently, neither the national clinical guidelines, nor the recommendations of RUSSCO, ESMO, NCCN provide indications and modes of adjuvant chemotherapy in the program of radical treatment of ampullary cancer. Therefore, in order to determine the indications for adjuvant chemotherapy, the relationship

between long-term survival and morphological features was studied. Based on the data obtained, the indications for adjuvant chemotherapy were determined: the growth of the ampullary tumor into the pancreas head, metastatic lesions of regional or juxta-regional lymph nodes, the presence of tumor emboli in the lymphatic or blood vessels. Based on the results of the ESPAC-3 study, Mayo regimen and gemcitabine monotherapy were adopted as medication regimens.

Four-six weeks after radical surgery, the following chemotherapy regimens were used: in 17 cases - Mayo regimen (5-fluorouracil 425 mg / m² i.v., jet + leucovorin 20 mg/m² i.v., jet, on the 1st - 5th days of the 28-day cycle, 6 cycles), in 30 cases - monotherapy with gemcitabine (1000 mg/m² on the 1st, 8th, 15th day with a break of 2 weeks, 4-6 courses).

Results

To assess the neoadjuvant treatment of pancreatic-biliary ampullary cancer, patients were grouped as follows – experimental group (n = 21) or control group (n = 48). In the experimental group, combined treatment was carried out, including preoperative remote RT, extended GPDR and adjuvant chemotherapy according to indications. In the control group, extended GPDR and adjuvant chemotherapy were performed according to indications. The groups studied postoperative complications, mortality, overall survival, average life expectancy.

The analysis of the studied groups showed no significant differences: sex (p = 0.5) and age (p = 0.6) distribution of patients, ECOG functional state (p = 0.8), ASA physical status (p = 0.3), the stage of the

tumor process (p > 0.05), the extent of surgical aid (p > 0.05), the type of anastomosis between the pancreas stump and the intestinal tube (p > 0.05), the duration of the operation (p = 0.9), intraoperative blood loss (p = 0.9), regimens of adjuvant chemotherapy (p = 0.9), i.e. the studied groups are identical.

In the experimental group, at the stage of RT, radiation injuries occurred in 6 (28.6%) cases: erythema in 4 (19.1%) cases, and leukopenia in 2 (9.5%) cases. Considering the table of acute radiation injuries (RTOG, 1995), grade 1 erythema was determined in all 4 cases. On average, erythema occurred on day 20.9 ± 1.84 (14-32) from the start of RT. To relieve itching and inflammation, the area of radiation damage was treated with mild steroid creams. On average, erythema disappeared without skin pigmentation in 6.8 ± 0.61 (4-10) days after the end of RT. Leukopenia developed in 2 cases at the RT stage. Considering the table of acute radiation injuries (RTOG, 1995), grade 1 leukopenia and grade 2 leukopenia were established in 1 case. Grade 1 leukopenia developed during the first sessions of external RT and persisted throughout the entire course of RT. This leukopenia was not specifically corrected. Grade 2 leukopenia developed after the fourth RT session. In order to correct leukopenia, a single injection of prednisolone 30 mg intramuscularly was performed. There was a positive dynamics and recovery of leukocytes within the laboratory norm before discharge (one day after the end of RT).

Postoperative complications in the groups are presented in Table 4.

Table 4

Postoperative complications in the groups

postoperative complications based on the Clavien-Dindo grades	experimental group, n=21	control group, n=48	intestinal type, n=43	total, n=112
<u>grade I</u>				
- wound suppuration	-	-	1 (2.33%)	1 (0.9%)
- hemorrhagic gastritis	-	-	1 (2.33%)	1 (0.9%)
- bilateral pneumonia	-	-	1 (2.33%)	1 (0.9%)
<u>grade IIIa</u>				
- pancreatic fistula, class A according to ISGPF	3 (14.3%)	7 (14.6%)	5 (11.6%)	15 (13.4%)
- pancreatic fistula, class AB according to ISGPF	-	3 (6.3%)	2 (4.65%)	5 (4.4%)
- liver abscess	-	1 (2.08%)	-	1 (0.9%)
- abscess of the abdominal cavity	2 (9.5%)	-	1 (2.33%)	3 (2.7%)
	p=0.9			
<u>grade IIIb</u>				
- pancreatic fistula, class AC according to ISGPF	-	1 (2.08%)	-	1 (0.9%)
- hepaticojejunostomy failure	-	-	1 (2.33%)	1 (0.9%)
- bilious peritonitis	-	1 (2.08%)	-	1 (0.9%)
- perforation of the small intestine	-	-	1 (2.33%)	1 (0.9%)
- acute intestinal obstruction	-	1 (2.08%)	-	1 (0.9%)
- biliary fistula	-	1 (2.08%)	-	1 (0.9%)
- abscess of the abdominal cavity	-	1 (2.08%)	-	1 (0.9%)
- subcutaneous eventration	-	-	1 (2.33%)	1 (0.9%)
	p=0.1			
<u>grade IVa</u>				
- erosive bleeding	-	3 (6.3%)	1 (2.33%)	4 (3.6%)
- intra-abdominal bleeding	-	1 (2.08%)	-	1 (0.9%)
- TELA	-	1 (2.08%)	-	1 (0.9%)

	p=0.1			
<u>grade V</u> - arrosive bleeding - postoperative peritonitis	1 (4.8%) -	- 3 (6.3%)	1 (2.33%) 2 (4.65%)	2 (1.8%) 5 (4.4%)
	p=0.8			
total	6 (28.6%)	24 (50.0%)	18 (41.9%)	48 (42.9%)
	p=0.09			

A retrospective analysis of the immediate results of surgical treatment of the main group and the group of clinical comparison showed that postoperative complications occurred in 6 (28.6%) and 24 (50.0%) cases, respectively.

Postoperative complications in the experimental group and control group were distributed as follows: grade IIIa complications, respectively 5 (23.8%) and 11 (22.9%; $p = 0.9$), grade IIIb complications - 0 and 5 (10.4 %; $p = 0.1$), grade IVa complications - 0 and 5 (10.4%; $p = 0.1$), grade V complications - 1 (4.8%) and 3 (6.3%; $p = 0.8$) observations. There were no significant differences in the structure and frequency of postoperative complications of the studied groups ($p = 0.09$).

Forty-eight (42.9%) of 112 cases radically operated for ampullary cancer developed complications

(Table 4). Analysis of the structure of postoperative complications showed that in the overwhelming majority they are represented by evasion of pancreatic secretion from the zone of pancreatojejunoanastomosis and complications arising against the background of this evasion - pancreatic fistula (18.7%), arrosive bleeding (5.4%), postoperative peritonitis (4.4%) and abdominal abscesses (3.6%).

A retrospective analysis of the immediate results of surgical treatment of the main group and the group of clinical comparison showed that mortality in the study groups was 4.8% (1 case) and 6.3% (3 cases, $p = 0.8$), respectively.

The causes of deaths in the groups are presented in Table 5.

Table 5

The causes of deaths in the groups

Cause of death	experimental group, n=21	control group, n=48	intestinal type, n=43	total, n=112
hemorrhagic shock	1 (4.8%)	-	1 (2.3%)	2 (1.8%)
multiple organ failure	-	3 (6.3%)	2 (4.7%)	5 (4.4%)
total	1 (4.8%)	3 (6.3%)	3 (7.0%)	7 (6.2%)
	p=0.8			

Seven (6.2%) of 112 cases radically operated for ampullary cancer died.

In 2 (1.8%) cases, the cause of death was hemorrhagic shock against the background of arrosive bleeding. Of these, in 1 case arrosion of the splenic artery wall was established and in 1 case - the left gastric artery. In 5 (4.4%) cases, the cause of death was

multiple organ failure associated with postoperative peritonitis. Of these, in 3 cases, the cause of postoperative peritonitis was pancreatic fistula of class C according to ISGPF and in 2 cases - recurrent perforation of the intestinal tube.

The overall survival rate of the groups is shown in Table 6.

Table 6

The overall survival rate of the groups

survival	intestinal type	experimental group	p	control group	ductal pancreatic head cancer, data of IROD*
1 year	100%	94.2%	0.004	51.9%	51.8%
2 years	93.3%	88.3%	<0.001	23.0%	19.8%
3 years	81.9%	82.2%	<0.001	13.1%	14.4%
5 years	61.3%	50.7%	0.01	9.8%	5.2%
7 years	42.5%	44.4%	0.01	6.5%	5.2%
10 years	42.5%	35.5%	0.05	6.5%	2.6%
average survival, months	60.5±9.15	74.8±12.58	0.0008	21.7±6.11	15.5±1.65

Note: * - data of the clinical material of the Irkutsk Regional Oncological Dispensary for 2006-2016 published in Practical Oncology. 2018; 19(4): 408-418. doi: 10.31917/1903408

Table 6 includes column No. 6 (in dark) with long-term survival rates for ductal cancer of the pancreas head (operable observations, where extended GPDR and adjuvant chemotherapy were performed).

The overall survival of the experimental and control group, respectively, was: 1 year - 94.2% and 51.9% ($p = 0.004$), 2 year - 88.3% and 23.0% (p

<0.001), 3 year - 82.2% and 13.1% ($p < 0.001$), 5 year - 50.7% and 9.8% ($p = 0.01$), 7 year - 44.4% and 6.5% ($p = 0.01$), 10 year - 35.5% and 6.5% ($p = 0.05$), average life expectancy - 74.8 ± 12.58 months and 21.7 ± 6.11 months ($p = 0.0008$).

A notable fact is that the traditional treatment regimen (radical surgery and adjuvant chemotherapy

according to indications) in patients with pancreatic-biliary type of ampullary cancer (control group) showed unsatisfactory long-term survival results, which are almost identical to the long-term survival results in pancreatic ductal cancer (see Table 6). The inclusion of preoperative radiation therapy in the radical treatment regimen made it possible to significantly increase the long-term survival rate in

pancreatic-biliary type of ampullary cancer (experimental group), which became commensurate with the long-term survival rate of radically treated intestinal type of ampullary cancer.

Relapse-free survival of patients with glandular ampullary cancer (n = 112) who received radical treatment in 2001-2019 in the Irkutsk Regional Oncological Dispensary is presented in Table 7.

Table 7.

Relapse-free survival of patients with glandular ampullary cancer who received radical treatment in 2001-2019.

survival	Stage I	Stage II	Stage III	Stage IV	All stages
1 year	90.0%	78.2%	81.9%	60.0%	77.8%
2 years	86.4%	57.8%	54.6%	23.5%	59.1%
3 years	78.7%	46.2%	54.6%	17.6%	51.0%
5 years	59.0%	33.7%	54.6%	0	35.2%
7 years	43.3%	33.7%	27.2%	0	27.4%
10 years	43.3%	33.7%	0	0	25.6%
average survival, months	79.2±11.86	37.7±7.37	28.2±15.20	14.5±4.89	44.7±5.44

Relapse-free survival was: 1 year - 77.8%, 2 years - 59.1%, 3 years - 51.0%, 5 years - 35.2%, 7 years - 27.4%, 10 years - 25.6%, average life expectancy - 44.7 ± 5.44 months.

Discussion

Ampullary cancer is a relatively rare heterogeneous malignant neoplasm, occurs in 6 cases per 1 million population, accounts for 0.2% in the structure of cancer of the digestive tract and 16.4% in the structure of cancer of the bile ducts.

Due to the anatomical features of the ampulla of Vater, the course of the disease and the development of the clinical picture, ampullary cancer is usually diagnosed at an early stage. Therefore, in more than half of the observations of primary treatment, it is possible to carry out a radical treatment regimen.

PDR is a standard surgery for ampullary cancer.

The data of the morphological study of our own clinical material show that the choice of the extent of the surgical aid (the depth of dissection) directly depends on the histological type of ampullary cancer. In the intestinal type and resectable tumor process, the standard PDR is a radical volume; three (7.1%) of 42 cases of intestinal type had metastases to juxta-regional lymph nodes detected. In the pancreatic-biliary type, various combinations of morphological signs (tumor growth in the MPVS, metastatic lesions of juxta-regional lymph nodes, perineural invasion, the presence of tumor emboli) amounted to 27 (39.7%) of 68 cases. Thus, the radical volume of the operation in the pancreatic-biliary type must be recognized as the extended GPDR.

Since half of all ampullary cancers recur after radical primary intervention, it is of paramount importance to identify and manage (appropriately) the features associated with the risk of disease recurrence. Currently, a group of unfavorable morphological signs has been identified and constantly revised, these are growth into surrounding organs and tissues, perineural invasion, metastatic lesions of lymph nodes, low tumor differentiation, etc., which determine an early relapse of the disease and a low life expectancy. The overwhelming majority of these prognostically unfavorable morphological signs are inherent in the

pancreatic-biliary type of ampullary cancer, i.e. histological type of ampullary cancer is an independent predictor of long-term survival; the overall 5-year survival rate for pancreatic-biliary and intestinal types is 27.5-53.3% and 61-73%, respectively. In our study, we compared long-term survival in the groups of pancreatic-biliary and intestinal types, where the radical treatment regimen included extended GPDR without neoadjuvant therapy. The overall 5-year survival rate and average life expectancy in the studied groups, respectively, were 9.8% versus 61.3% ($p < 0.001$) and 21.7 ± 6.11 months against 60.5 ± 9.15 months ($p = 0.0007$).

The high relapse rate is a strong argument for considering multimodal treatment for ampullary cancer.

Currently, the data on the effectiveness of the use of adjuvant therapy in the radical treatment regimen for ampullary cancer are contradictory.

ESPAC-1 (1997) of cases with R0 resection revealed the median survival in groups with and without adjuvant chemotherapy equal to 15.9 months against 16.9 months, respectively. According to the results of EORTC-40891 (1999), the 2-year survival rate for ampullary cancer in the control group and the group of adjuvant chemotherapy was 63% and 67%, respectively ($p = 0.737$). ESPAC-3 (v2, 2016), for ampullary cancer, revealed the median survival in the control group and the combination treatment group, respectively, equal to 34 months and 57 months, respectively. According to B.L. Ecker et al. (2019) regardless of the stage of the tumor process, the severity, the presence/absence of tumor cells at the edge of the resection, the presence/absence of metastatic lesions of the lymph nodes, histological type, adjuvant therapy does not play any role in improving overall survival in patients with FS cancer. According to M. Al-Jumayli et al. (2019) adjuvant therapy did not change relapse-free and overall survival rates. The 5-year survival rate was 22.7%.

Analysis of a large sample of NCDB showed the following. Group with adjuvant chemotherapy and without adjuvant chemotherapy: median overall survival was 47.2 and 35.5 months, 1-year survival - 90% and 85%, 3-year - 57% and 49%, 5-year - 44% and 38%, respectively. It was stated that adjuvant chemotherapy significantly increased life expectancy in the group with the T3/T4 index. Group with adjuvant chemotherapy and without adjuvant chemotherapy: median overall survival was 38.1 months, respectively. versus 31.0 months, 1-year survival rate - 88% versus 83%, 3-year survival rate - 51% versus 45%, 5-year survival rate - 40% versus 35%. Adjuvant CRT significantly increased life expectancy in the group with metastatic lymph node involvement. A recent series from the Mayo Clinic (2018) demonstrated the benefit of adjuvant chemotherapy in stage IIB or higher. According to the data obtained, a 55% reduction in the risk of death was noted in patients with advanced disease receiving adjuvant therapy [HR: 0.45, (95% CI: 0.22–0.93), $P = 0.03$]. Similar encouraging results were obtained in another retrospective series, which collected data from the National Database, including 4190 patients with ampullary cancer. There was a 18% reduction in the risk of death [HR: 0.82, (95% CI: 0.71–0.95)], which is typical for large tumors and advanced stages. In our study, we used two modes of adjuvant chemotherapy (based on the results of the ESPAC-3 study): Mayo and gemcitabine monotherapy. We do not consider these chemotherapy regimens to be successful for ampullary cancer. Probably, in the future, chemotherapy regimens for the pancreatic-biliary type will be represented by various combinations of 5-FU, gemcitabine and capecitabine; for the intestinal type, the FOLFOX regimen is possible.

Neoadjuvant treatment is represented by single observations in the form of retrospective reports (Yeung R.S. et al., 1993; Hoffman J.P. et al., 1998; Palta M. et al., 2011). Randomized controlled trials are absent. Nevertheless, the authors noted a high frequency of grade 4 treatment pathomorphosis (80–100%) in the removed specimens, partial (67%) and complete (28%) tumor response. Considering the above and agreeing with the opinion of C.G. Willett et al. (1993) that preoperative RT will reduce the risk of dissemination of cancer cells during surgery, we conducted a single-center retrospective prospective study to evaluate the combined treatment of pancreatic-biliary type of ampullary cancer. The overall 5-year survival rate and average life expectancy in the groups of combined treatment (preoperative RT and extended GPDR) and extended GPDR without preoperative RT, respectively, were 50.7% versus 9.8% ($p = 0.01$) and 74.8 ± 12.58 months versus 21.7 ± 6.11 months ($p = 0.0008$). The relatively small number of observations with the discussed nosology did not allow us to compare the long-term survival rate taking into account the stages of the tumor process.

The above studies of neoadjuvant treatment of ampullary cancer pay little attention to the damage to

radiation therapy, methods of control and drug correction of these pathological conditions. R.S. Yeung et al. (1993) reported that the diagnosed toxicity was represented by febrile neutropenia (in 2 cases), biliary sepsis (in 2 cases), nausea and vomiting. One patient died of biliary sepsis prior to completion of CRT. J.P. Hoffman et al. (1998) the problem of the safety of neoadjuvant therapy was not discussed, probably due to the small number of observations. M. Palta et al. (2012) bypassed the topic of chemotherapy toxicity, noting only the disadvantages - the preoperative time interval during which the patient's condition may worsen, the disease progresses, which excludes subsequent surgical intervention. In our study, during remote radiotherapy, radiation injuries occurred in 28.6% of cases: grade 1 erythema - in 19.1%, grade 1 leukopenia - in 4.75%, and grade 2 leukopenia - in 4.75% of cases. The above-mentioned injuries of radiation therapy were arrested against the background of conservative therapy for a short period of time, in particular, erythema within 4–10 days from the moment of completion of radiation therapy, leukopenia - one day after completion of radiation therapy, and did not increase the duration of the preoperative period.

To finalize the discussion we should say that there are no malignant neoplasms insensitive to radiation therapy. Achievement of therapeutic effect requires selecting correctly the type of ionization radiation, the method and dose of energy supply to the focus, the sequence for combined treatment. The same applies to drug therapy, it is necessary to choose the right chemotherapy regimen. As for the contradictory data regarding the effectiveness of the above therapy, the reason probably lies in the study protocol itself and its components, namely, the retrospective nature of the study, a small number of observations in ongoing studies (due to the rarity of the discussed nosology), the heterogeneity of the compared groups by histological type of ampullary cancer and disease neglect (patients who received adjuvant therapy after PDR have more advanced disease), lack of proper control of chemotherapy regimens, differences in the volume of operations (mainly due to the depth of dissection), etc. For correct conclusions, a multicenter randomized controlled trial is required.

Intestinal and pancreatic-biliary types of ampullary cancer are two different tumor processes with different tumor biology, local manifestations, drug sensitivity and disease prognosis. The pancreatic-biliary type is morphologically, immunohistochemically and clinically similar to ductal cancer of the pancreas and assumes the same type of treatment regimen represented by neoadjuvant therapy and appropriate chemotherapy regimens. The intestinal type is morphologically and clinically similar to colorectal cancer, showing tropism for similar drugs. This is the second strong argument for starting a multicenter randomized controlled trial to confirm these claims.

Abbreviations

GPDR	- gastropancreaticoduodenal resection
RT	- radiation therapy
MPVS	- mesentrico-portal venous system
PDR	- pancreaticoduodenal resection
P	- pancreas
rLa	- right liver artery
AV	- ampulla of Vater
CT	- chemotherapy
CRT	- chemoradiotherapy

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ГЕМОПЕРФУЗИЯ ПРИ ОСТРОМ ОТРАВЛЕНИИ ПСИХОТРОНЫМИ ПРЕПАРАТАМИ

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HEMOPERFUSION IN ACUTE PSYCHOTROPIC POISONING

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Аннотация. Представлено комплексное лечение пациентки с острым отравлением амитриптилином и циклодолом с применением энтеросорбции, кишечного лаважа и гемосорбции на новой колонке с синтетическим сорбентом. Для гемосорбции использована колонка с двухслойным синтетическим полимером, разработанная для селективной сорбции цитокинов методом прямой гемоперфузии. Количественные определения уровней амитриптилина и циклодолом до колонки и после колонки, а также до гемосорбции и после гемосорбции показали высокую эффективность сорбента по удалению токсиканта из крови. Применение 6 часовой гемосорбции позволило снизить уровень амитриптилина от исходного более чем в 4 раза и уровень циклодолом - более чем в 3 раза до терапевтических уровней и получить выраженный положительный клинический эффект в комплексном лечении пациентки с тяжелым отравлением.

Summary. Presented is a complex treatment of a patient with acute amitriptyline and cyclodole poisoning using enterosorption, intestinal lavage and hemosorption on a new column with a synthetic sorbent. For hemosorption, a column with a two-layer synthetic polymer was used, developed for selective sorption of cytokines by direct hemoperfusion. Quantitative measurements of levels of amitriptyline and cyclodole before and after the column, as well as before haemosorption and after haemosorption, showed a high effectiveness of the sorbent in removing toxicant from the blood. The use of 6-hour hemosorption allowed to reduce the level of amitriptyline from the initial by more than 4 times and the level of cyclodole by more than 3 times to therapeutic levels and obtain a pronounced positive clinical effect in the complex treatment of a patient with severe poisoning.

Ключевые слова: острое отравление, амитриптилин, циклодол, гемосорбция.