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OPTIMIZING THE PANCREATIC-DIGESTIVE ANASTOMOSIS IN PATIENTS WITH PANCREATICODUODENAL RESECTION

AUTHOR'S ABSTRACT

for awarding the educational and scientific degree "**Doctor**" in professional field 7.1. Medicine, doctoral programme "General Surgery" and scholarly subject/major "General Surgery"

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The dissertation consists of 136 typed pages and is illustrated by means of 58 charts and 43 figures. The list of cited literature includes 205 titles, of which 21 in Cyrillic and 184 in Latin.

The dissertation has been discussed and refered for public defense at an extended Department Council of the Department of Surgical Diseases at the Medical University of Pleven on the grounds of Art. 24, par. 6 and Art. 30, par. 3 of the Act for the Development of the Academic Staff in the Republic of Bulgaria and Art. 39, par. 1 of the Rules for the development of the academic staff at the Medical University of Pleven in connection with Decision of Academic Council (Protocol No 21/27.02.2023).

The public defense of the dissertation will take place on June 30 at 1:30 p.m. in hall Ambroise Pare, Telecommunication Endoscopic Centre of the Medical University of Pleven on the grounds of Order No 715 from 01.03.2023 by Prof. Dobromir Dimitrov Dimitrov, MD, PhD, Rector of Mu-Pleven, in front of a scientific jury in the following composition:

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The defense materials have been published on the website of the Medical University of Pleven: http://mu-pleven.bg

CONTENTS

ABBREVIATIONS

BL - biliary leaks
GJA - gastro-jejuno anastomosis
ERCP - endoscopic retrograde cholangiopancreatography
DSE - delayed stomach emptying
IAA - intra-abdominal abscess
IAI - intra-abdominal infection
IAH - intra-abdominal hemorrhage
Insuf PA - insufficiency of pancreatic anastomosis
PA - pancreatic anastomosis
PGA - pancreatic gastric anastomosis
PGA-MIX DRAIN – PGA with mixed drain
PDA - pancreatic-digestive anstomosis
PDR - pancreaticoduodenal resections
PJA - pancreaticojejunal anastomosis
PJA - EXT DRAIN - PJA with external drain
PF - pancreatic fistula
WI – wound infection
HJA - hepaticojejunostomy
T-L - termino-lateral
T-T - termino-terminal

1. INTRODUCTION

Pancreatic cancer is the fourth leading cause for death from oncologic diseases worldwide. The overall five-year survival rate is between 5.0% and 21.0 %. Radical surgery is the only possibility for definitive treatment, but it is possible only in 15.0÷20.0% of the cases. The percentage of survivors is too low, due to the high post-operative mortality rate and the high percentage of carcinoma diagnosed late. At the time of giving the diagnosis of cancer in the head of the pancreas, 33.0% of the diseased already have distant metastases, and in case of cancer in the body and head of the pancreas – 75% (19). The average life expectancy of irresectable patients is 6.0÷7.0 months. The only patients, who stand a chance of definitive recovery are those with cancer localization in the head of the pancreas and the periampullary area. Their joint examination has been prompted by their similar medical history and the identical diagnostic and surgical tools used, despite the fact that cancer in the periampullary area has different origin, slower evolution and better prognosis.

Proximal pancreaticoduodenal resection (PDR), developed by A. O. Whipple and co-authors in 1935, is a contemporary surgical methodology for treatment of cancer in the head of the pancreas and the periampullary area. The biggest advantage of this surgical procedure is the radicality of the treatment. The main disadvantage, irrespective of the type of the conducted pancreatic-digestive anastomosis (PDA) is the high risk for the occurrence of pancreatic fistula (in up to 30.0% of cases). Despite the fact that over 80 optimized surgical techniques for performing PDA have been published since then, anastomosis remains physiologically burdened. Consequently, the percentage of early complications remains high for the contemporary standards of radical treatment. The most important factor, influencing the function of the remaining pancreas is the integrity of the PDA, the mechanical unburdening of which is a prerequisite for better clinical effect.

The new surgical strategy, object of this clinical study, is a general concept, which aims at reducing the mechanical burdening of PDA by means of an optimized approach of reconstruction and optimized method of drainage following PDR.

At present the main disadvantage of anastomosis techniques – termino-lateral pancreaticojejunal anastomosis (TL-PJA) or termino-lateral gastro-jejuno anastomosis (TL-GJA) comes down to the fact that they strengthen PDA anatomically, but it remains physiologically burdened and although partially diminished, the risk of pancreatic fistula (PF) remains comparatively high. In the Whipple operation TL-PJA remains to a high extent mechanically burdened by the passage of the gastrointestinal contents. This is due to the type of reconstruction of these two digestive anastomoses, mentioned above. The newly created PDA disrupt the physiological “horseshoe-shaped” anatomic configuration between the stomach and the small intestine, ensuring the movement of the passage with minimal mechanic resistance. These anastomoses are “two-looped” and with blindly ending postresective stumps – small intestine, up to T-L PJA, and stomach – up to T-L GJA. On the one hand, in the Whipple operation the new anatomic reconstruction does not have the physiological “horseshoe” shape, ending blindly at the level of T-L PJA or the termino-terminal (TT) PJA. On the other hand, the gastric stump to T-L GJA creates a significant mechanical resistance to the passage of the gastrointestinal contents. Third, when the gastric and small intestine postresective paresis is added to these obstacles, the end result is an impeded movement of the passage and mechanical burdening of the newly created PDA, and what is more – most significantly - at GJA. Replacing T-L PJA with T-L pancreatic gastric anastomosis (PGA) gives an opportunity, on the one hand, to facilitate the technical implementation and make it safer and on the other hand – to significantly recover the “horseshoe” anatomic configuration between the stomach and the small intestine by ensuring that the gastrointestinal passage moves at one level, without falling in blindly-ending sections. Unburdening is insufficient, since the gastric stump to T-L GJA exerts mechanical resistance. The drainage techniques used so far improve the strengthening of the drains and the outflow of drain contents. The drainage of each PDA is autonomous. The main disadvantage is their percutaneous guidance through the abdominal cavity and the inadequate evacuation of gastrointestinal contents, whereas upon their removal the frequency of PF diminishes, but remains high.

This constitutes grounds for us to conduct this complex research into patients with pancreatic cancer.

2. GOAL AND TASKS

The **goal** of this dissertation is to optimize PDA through PGA with mixed drainage and to reduce the early post-operative complications in patients with pancreatic cancer and cancer in the periampullary area subjected to PDR.

To achieve this goal we have undertaken the following **tasks**:

1**.** Randomizing the examined groups of patients – with PJA with external drainage (PJA-EXT DRAIN) and with PGA with mixed drainage (PGA-MIX DRAIN).

2. Determining the total mortality rate, total morbidity rate and the average time for hospitalization of those two groups of patients (PJA-EXT DRAIN and PGA-MIX DRAIN).

3. Determining the relative share of early post-operative complications (within one month) in those two groups of patients (PJA-EXT DRAIN and PGA-MIX DRAIN).

4. Determining the relative risk for occurrence of early post-operative complications (within one month) in those two groups of patients (PJA-EXT DRAIN and PGA-MIX DRAIN).

5. Reducing the mechanical burdening of PDA by optimizing the reconstruction and drainage of digestive anastomoses following PDR.

3. MATERIAL AND METHODS

3.1. Material

Subject and object of the research

The subject of the research is the surgical treatment of pancreatic cancer and cancer in the periampullary area with PDR. The object of research includes patients with pancreatic cancer and cancer in periampullary area with indications for surgical treatment. The research is based on the epidemiological approach and it is experimental-theoretical. As regards the exact moment of data collection this is an observatory, analytical and cohort research.

The examined group has been determined prospectively. Over a ten-year period (2007-2017) at the MBAL (multi-profile hospital for active treatment) Sveta Anna AD Varna 40 proximal PDR with PGA-MIX DRAIN were carried out at random. The control group was determined retrospectively by using the registers of Onco-dispensary VARNA REGION for the same period. A total of 710 patients with carcinoma in the pancreatic gland, 371 men and 339 women, were hospitalized at the dispensary. Out of 275 patients with surgical treatment, a random sample of 80 patients with PDR and T-L PJA-EXT DRAIN was taken, who were randomized by epidemiological indicators with the examined group. This sample is formed by means of a simple random and irreversible selection. The patients have been diagnosed preoperatively and postoperatively both by means of routine laboratory methods (hemogram, cholestasic indicators, cytolitic enzimes, albumin and total protein,CA 19-9) and by modern methods of image diagnostics (ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography – ERCPG, fibrogastroduodenoscopy, gastrography, cardiopulmonary monitoring).

Exclusion criteria include: cancer localization in the body and tail of the pancreas; total or subtotal pancreatectomy and distal PDR.

The efficiency of the surgical procedure is determined by the frequency of occurred (till the end of the first month) postoperative complications, the relative risk for their occurrence and the duration of hospitalization. The risk for the occurrence of early complications, related to the type of surgical procedure (PJA-EXT DRAIN and PGA-MIX DRAIN) directly measures the efficiency of cancer treatment in the pancreatic glands and the periampullary area. The examined early complications are pancreatic insufficiency (Insuf PA), PF, intra-abdominal abscess (IAA), intraabdominal hemorrhage (IAH), intraabdominal infection (IAI), gastroparesis and delayed stomach emptying (DSE), wound infection (WI) and biliary leak (BL). The postoperative mortality of the patients is also examined.

By means of a cohort (group) examination the patients were selected on the basis of the existence (cases) and lack (controls) of such complications. The proportions were reported of patients in both groups, exposed to the risk factor – the type of surgical procedure (PJA-EXT DRAIN/PGA-MIX DRAIN).

The relative comparison of occurrences in both groups of patients has been used to calculate the risk for emergence of complications when comparing the clinical effect of PGA-MIX DRAIN with that of PJA-EXT DRAIN.

3.2. Methods

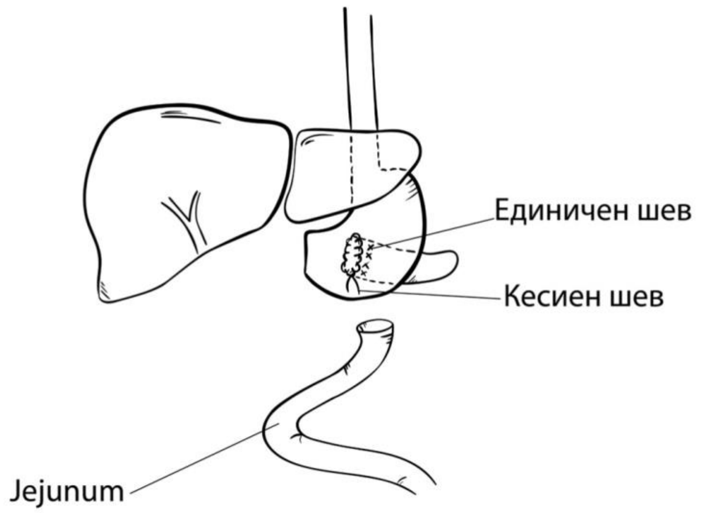
3.2.1. Surgical methods – PDR methodology

The new surgical strategy of this clinical research aims at reducing the mechanical burdening of PDA by applying an optimized approach of reconstruction and optimized approach of drainage of digestive anastomoses following PDR.

<u>Optimized approach to reconstruction of digestive anastomoses</u>

PDR is carried out in line with the Whipple operation, with the following sequence of resectioned organs: antrectomy of 5-7 cm of the pylorus; resection of the head and neck of the pancreas; cholecystectomy with resection of the distal common duct and resection of distal duodenum and jejunum at 5 cm of *lig. Treitz*.

The scheme of the PGA reconstruction is presented in fig. 3.2.1, and the one of the drainage of digestive anastomoses with bicameral nasogastric probe during the second stage – in fig. 3.2.2 and fig. 3.2.3.



single suture/purse-string suture

Fig. 3.2.1. Scheme of PGA reconstruction

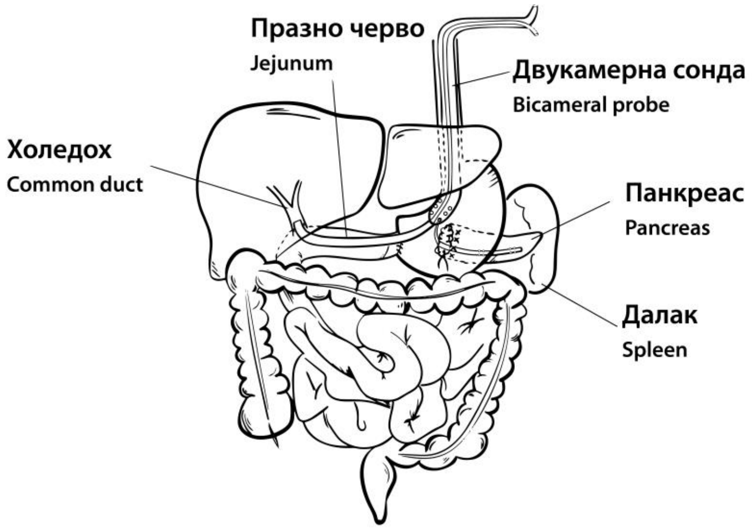


Fig. 3.2.2. Scheme of drainage of digestive anastomoses with bicameral nasogastric probe

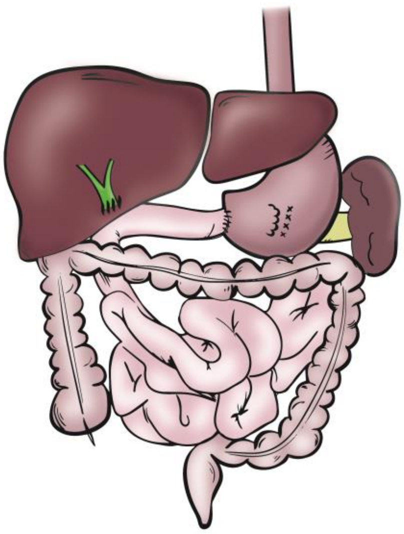


Fig. 3.2.3. Scheme of reconstruction following pancreatic-duodenal resection

As compared to the Whipple operation, the optimized approach to reconstruction of digestive anastomoses involves:

1. Replacement of T-L PJA with T-L PGA. 2. Replacement of T-L GJA with T-T GJA.

The reconstruction of digestive anastomoses is carried out at three main stages in the following order: 1. T-L PGA; 2. T-L hepaticojejunostomy (HJA) and 3. T-T GJA.

The stages of operative reconstruction are illustrated in fig. 3.2.4 – fig. 3.2.12.

I stage: T-L PGA

1. About 2-3 cm of the resected end of the pancreas are dissected. An opening is made at the posterior abdominal wall, corresponding to the diameter of the pancreatic stump, but not smaller than 0.5 cm. A drain is placed in the pancreatic duct, depending on the diameter of the duct and is fixed by slowly absorbable sutures.

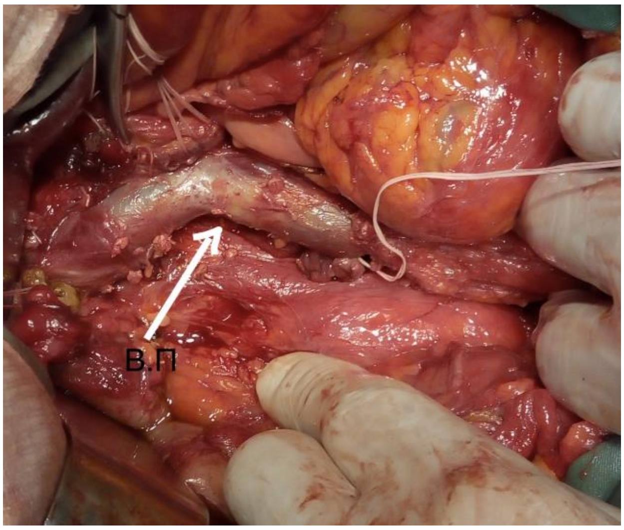


Fig. 3.2.4. Native photography of the stage following PDR

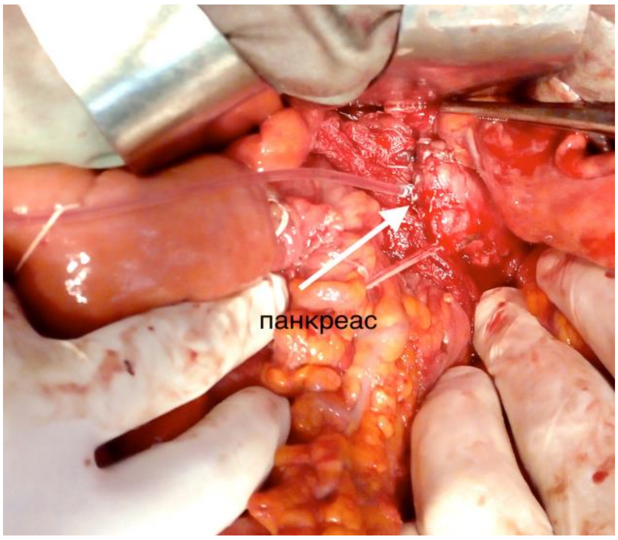


Fig. 3.2.5. Native photography of the stage of draining ductus pancreaticus

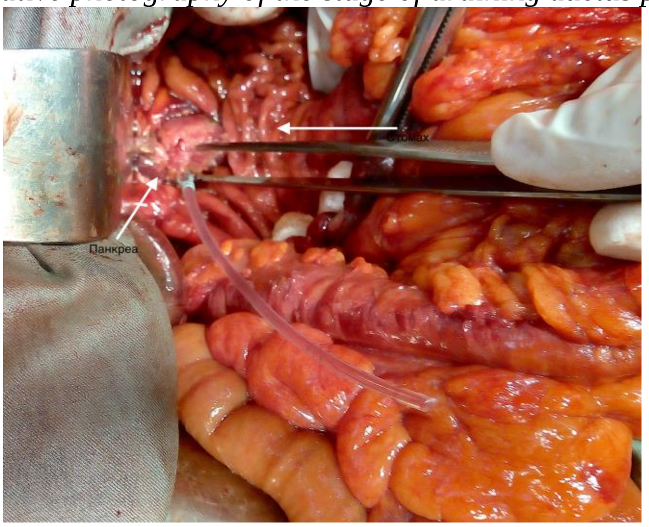


Fig. 3.2.6. Native photography of the stage of PGA

2. A purse-string suture is performed along the posterior abdominal cavity at the point of the opening – PDA or BIOSYN 3-0.

3. Single sutures are performed, 4-5 in number, along the posterior abdominal cavity and the capsule along the anterior pancreatic wall.

4. Invaginating the pancreatic stump in the stomach – 1-2 cm.

5. Tightening up the purse-string suture and the single sutures.

6. Fixing the posterior pancreatic wall to the posterior abdominal wall by single sutures, 4-5 in number - BIOSYN 3-0 or PDS.

II stage: Т-Л ХЙА T-L HJA

1. Positioning the jejunum. The proximal part of the jejunum goes transmesocolically past the common duct and reaches the remainder of the stomach. A section of the intestine is always left, which is approximately 5 cm longer, as compared to the distance between the common duct and the stomach, so as to avoid tension.

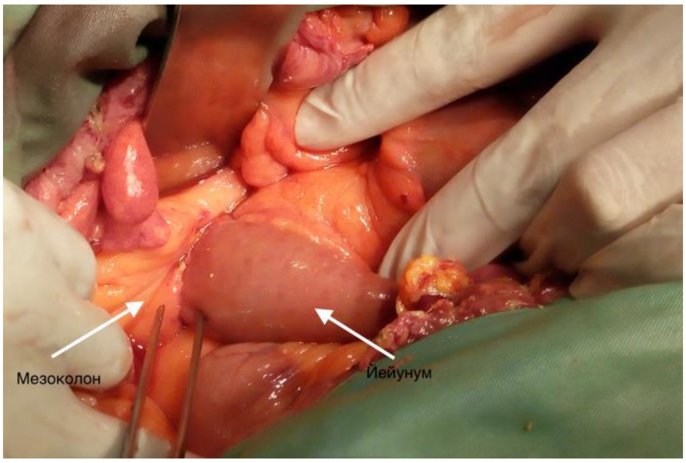


Fig. 3.2.7. Native photography of the stage of retrocolic passage of the small intestine

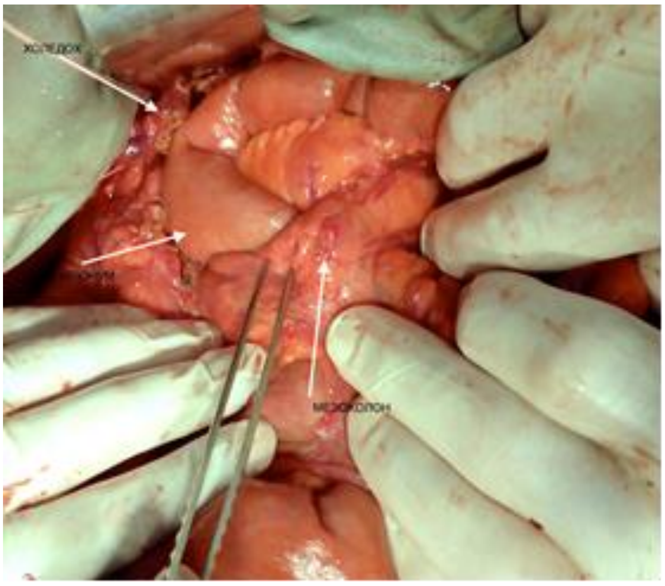


Fig. 3.2.8. Retrocoloic passage of jejunum for the purpose of preparation for HJA

2. Constructing the posterior wall of the anastomosis, whereas the posterior wall of the common duct is fixed by single sutures to the small intestine.

3. Placing bicameral nasogastric probe, which comes out through the stomach stump, passes through the small intestine that was taken out and reaches the common duct, as its end enters into the common duct by 2-3 cm and is fixed along the posterior wall of HJA by single quickly absorbable suture.

4. Constructing the anterior wall of the anastomosis.

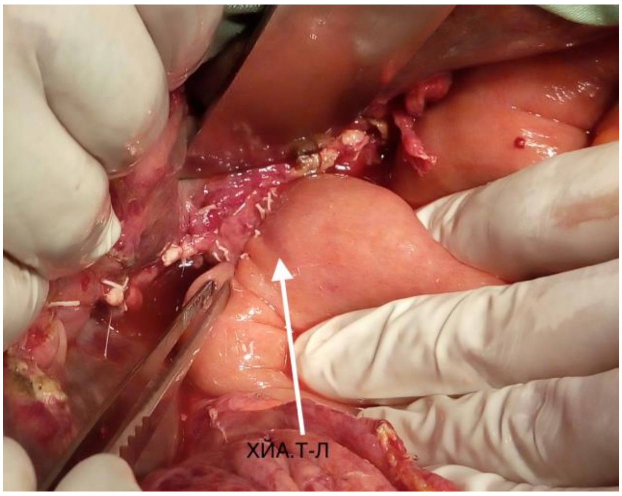


Fig. 3.2.9. Native photography of the stage of T-L HJA

III stage: T-T GJA

1. The pancreatic drain in the bicameral nasogastric probe is implanted in the lumen of the abdomen or it remains free in the lumen of the abdomen.

2. Closing the remainder of the stomach from the lesser curvature to the greater curvature by means of a linear suturing device, leaving a resected section from the greater curvature, which in size corresponds to the lumen of the intestine.

3. Inspection for localizing the openings of the bicameral nasogastric probe in the fundus of the stomach close to the pancreatic stump.

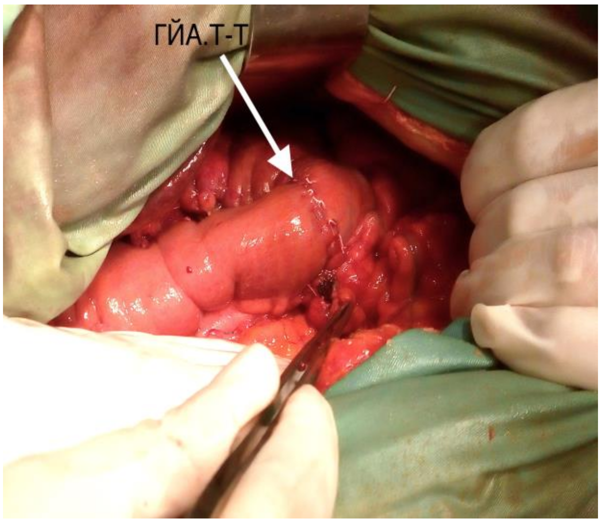


Fig. 3.2.10. Native photography of the stage of T-T GJA

Next, the final digestive anastomosis is built, two-level T-T GJA with single sutures or continuous suture. The reconstruction ends with truncal vagotomy.

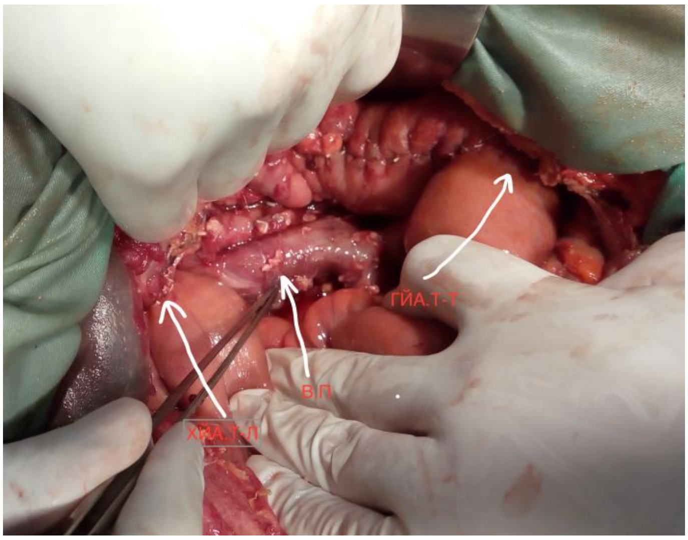


Fig. 3.2.11. Native photography of the final stage of T-T GJA and T-L HJA

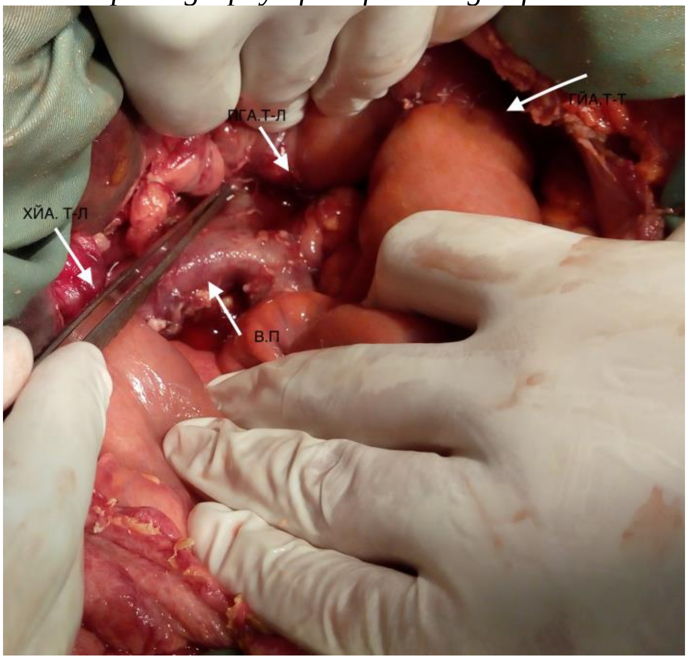


Fig. 3.2.12. Native photography of the final stage of T-L PGA, T-T GJA and T-L HJA

By building one loop of T-L PGA, T-L HJA and T-T GJA the "horse-shoe shaped" anatomic configuration is restored between the stomach and the small intestine and the gastrointestinal passage moves on one level without falling into blind sections. By building a T-T GJA the stomach stump is removed, which exerts mechanical resistance to the passage in T-L GJA according to the Whipple operation.

Fig. 3.2.13 shows a postoperative gastrography with contrast medium in the newly created GJA.

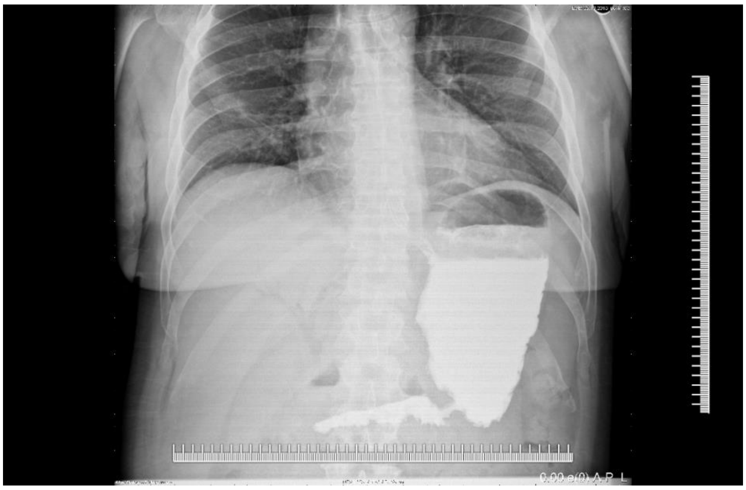


Fig. 3.2.13. Postoperative gastrography with contrast substance in GJA

Optimized method for drainage of digestive anastomoses

Unlike the Whipple operation, the optimized method for drainage of digestive anastomoses in this research includes the insertion of a drain in the pancreatic duct.

We insert a drain in the pancreatic duct and replace the percutanesously moved out of the abdominal cavity drains with a bicameral nasogastric probe especially constructed for the purpose, which enables a joint intraluminal drainage of the three digestive anastomoses – TL PGA, TL HJA and TT GJA. The nasogastric probe is aspirated during the first 24 hours with a syringe of 50 mL in every 4 hours, and between the 24^{th} hour following the operation and the 48^{th} hour – in every 6 hours. The nasogastric pump is aspirated only by means of a syringe and under no circumstances – by means of a vacuum pump. It is taken out in the period between 12 hours and 24 hours following the recovery of the passage. This recovery most often takes place between the second and the fourth day.

3.2.2. Statistical methods

The data have been processed and analyzed with IBM SPSS Version 19.00 for Windows. To verify the statistical hypotheses when working with SPSS an error has been used of type I, equal to 0.05 (α=0,05). For assessment the level of significance was used, which comprises the respective likelihood of the estimated empiric characteristic. The level of significance has been compared to the error α=0.05. If the level of relevance is lower than α (<0.05), the null hypothesis (Ho) is rejected and the alternative one (Ha) is acknowledged as correct. Statistical methods have been used for quantity and quality assessment of the factor impact and statistical verification of hypotheses. To verify the theoretical allocation of the studied variable the Kolmogorov–Smirnov test was used. It is used to verify whether the allocation of the studied variable is normal. To prove the causal link in a normal allocation of the studied variables parametric tests are used and when normal allocation is lacking – non-parametric tests. If the level of relevance is <0.05 the alternative hypothesis is confirmed, i.e. the link between the studied variables is statistically significant.

To prove the causal link, the following statistical methods have been used: variation analysis – Fisher's exact test; correlation analysis – the Pearson χ^2 test, as well as Mann-Whitney's non-parametric test. When the studied link is statistically significant, the degree of this link is measured by means of Cramer's correlation coefficient: with values 0,1÷0,2 it is considered weak, with 0,3÷0,4 – moderate, with 0,5÷0,6 – significant, with 0,7÷0,9 - big, and over 0,9 – exceptionally big. When the causal link is proven, the "odds ratio" method is used to assess the studied factor as a risk factor. To characterize the centre of the empiric allocation of the studied variables, the following summarizing characteristics have been determined: arithmetic average value and a median.

In case of greater deviations from the normal distribution and the existence of outliers as an alternative to the ordinary average and median the so called weighted sustainable assessments have been determined. Huber's M-estimator, and in case of significant deviations - Tukey's methods, Hampel's M-estimator and Andrew's wave.

4. OWN RESULTS

4.1. Randomizing the studied groups of patients

The studied group with PGA-MIX DRAIN: optimized PDR with optimized drainage: T-L PGA, T-L HJA and T-T GJA; intraluminal drainage of three digestive anastomoses with bicameral nasogastric probe.

Control group with PJA-EXT DRAIN: classical PDR under Whipple with external drainage: T-L PJA, T-L HJA, T-L GJA; separate external drainage of anastomoses, taken out through the anterior abdominal wall.

Table 4.1.1. Allocation of patients according to type of PA

PA	n	%
PJA-EXT DRAIN	80	66,7
PGA-MIX DRAIN	40	33,3
Total	120	100,0

<u>Structure of the studied groups of patients</u>

The allocation of patients by gender and age can be seen in tables 4.1.2 and 4.1.3.

Table 4.1.2. Allocation of patients by gender

Sick		Type of PA		Total
		PJA-EXT DRAIN	PGA-MIX DRAIN	
men	Number	46	21	67
	Valid % type PA	57,5%	52,5%	55,8%
women	Number	34	19	53
	Valid % type PA	42,5%	47,5%	44,2%
Total	Number	80	40	120
	Valid % type PA	100,0%	100,0%	100,0%

Table 4.1.3. Allocation of patients by age (M-average)

	Type of PA	Huber	Tukey	Hampel's	Andrew
Age	PJA-EXT DRAIN	66,89	66,86	66,63	66,86
	PGA-MIX DRAIN	65,87	65,94	65,88	65,93

Allocation of patients according to the main clinical symptoms are shown in tables 4.1.4. – 4.1.9.

Allocation of patients with jaundice can be seen in tables 4.1.4.

Table 4.1.4. Allocation of patients with jaundice

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
Jaundice	with	Number	55	35	90
		Valid % type PA	68,7%	87,5%	75,0%
	without	Number	25	5	30
		Valid % type PA	31,3%	12,5%	25,0%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%

Allocation of patients with epigastric pain is shown in table 4.1.5.

Table 4.1.5. Allocation of patients with epigastric pain

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
Epigastric pain	with	Number	52	28	80
		Valid % type PA	65,0%	70,0%	66,7%
	without	Number	28	12	40
		Valid % type PA	35,0%	30,0%	33,3%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%

Allocation of patients with weight loss is shown in table 4.1.6.

Table 4.1.6. Allocation of patients with weight loss

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
Weight loss	with	Number	53	32	85
		Valid % type PA	66,3%	80,0%	70,8%
	without	Number	27	8	35
		Valid % type PA	33,7%	20,0%	29,2%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%

The allocation of patients with nausea and vomiting is illustrated in table 4.1.7

Table 4.1.7. The allocation of patients with nausea and vomiting

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
Nausea	with	Number	45	25	70
		Valid % type PA	56,3%	62,5%	58,3%
	without	Number	35	15	50
		Valid % type PA	43,7%	37,5%	41,7%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%

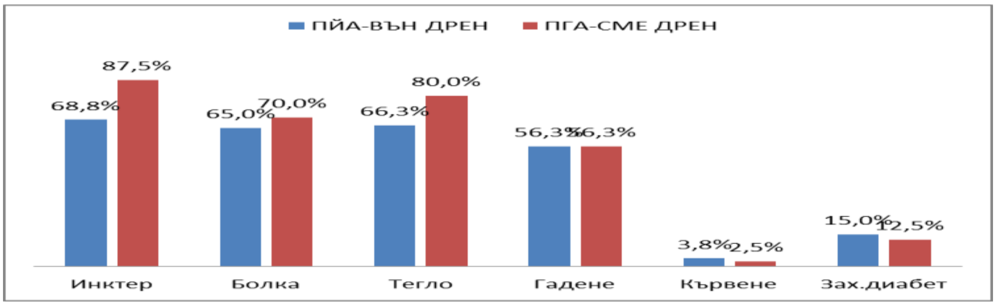
Allocation of patients with gastrointestinal bleeding (GI) can be seen in table 4.1.8, and the patients with sugar diabetes - in table 4.1.9.

Table 4.1.8. Allocation of patients with gastrointestinal bleeding (GI)

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
GI bleeding	with	Number	3	1	4
		Valid % type PA	3,7%	2,5%	3,3%
	without	Number	77	39	116
		Valid % type PA	96,3%	97,5%	96,7%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%

Table 4.1.9. Allocation of patients with sugar diabetes

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
Sugar diabetes	with	Number	12	5	17
		Valid % type PA	15,0%	12,5%	14,2%
	without	Number	68	35	103
		Valid % type PA	85,0%	87,5%	85,8%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%



Jaundice Pain Weight Nausea Bleeding Sugar diabetes

Fig. 4.1.1. Frequency of symptoms in PJA-EXT DRAIN and PGA-MIX DRAIN PJA-EXT DRAIN (blue), PGA-MIX DRAIN (red)

Fig. 4.1.1 illustrates the comparison between the frequency of specific clinical symptoms in the two types of PA – PJA-EXT DRAIN and PGA-MIX DRAIN.

The allocation of patients, examined with endoscopic retrograde cholangiopancreatography ERCPG can be seen in table 4.1.10.

Table 4.1.10. Allocation of patients with ERCP

			Type of PA		Total
			PJA-EXT DRAIN	PGA-MIX DRAIN	
ERCP	with	Number	10	6	16
		Valid % type PA	12,5%	15,0%	13,3%
	without	Number	70	34	104
		Valid % type PA	87,5%	85,0%	86,7%
Total		Number	80	40	120
		Valid % type PA	100,0%	100,0%	100,0%

The allocation of patients according to the main characteristics of pancreatic cancer have been systematized in tables 4.1.11 – 4.1.14.

Table 4.1.11 illustrates the allocation of patients with pancreatic adenocarcinoma according to the initial localization of the tumor, table 4.1.12 – according to the structure of the pancreatic parenchyma, table 4.1.3 – according to the TNM stage of the humor and table 4.1.14 – according to the degree of tumor differentiation G.

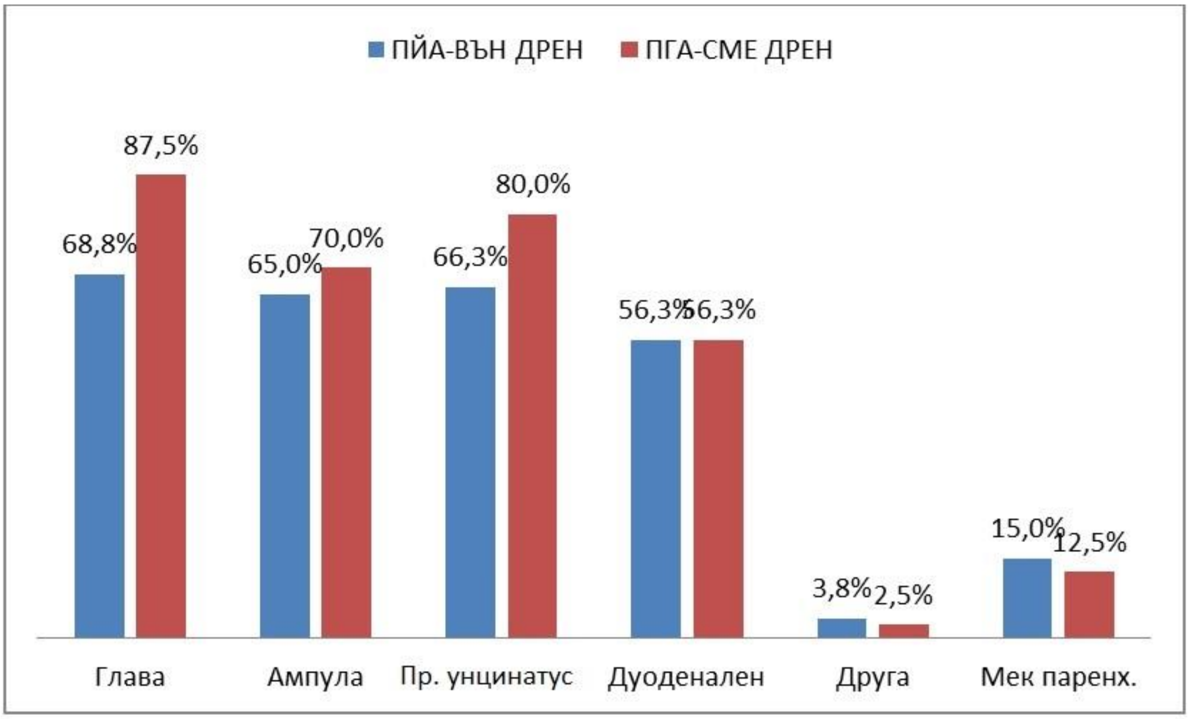
Table 4.1.11. Allocation of patients according to the initial localization of adenocarcinoma

Localization of adenocarcinoma		Type of PA		Total
		PJA-EXT DRAIN	PGA-MIX DRAIN	
Head of the pancreas	Number	27	16	43
	Valid % type PA	33,8%	40,0%	35,8%
Ampulla of pancreas	Number	25	11	36
	Valid % type PA	31,3%	27,5%	30,0%
Processus uncinatus	Number	8	4	12
	Valid % type PA	10,0%	10,0%	10,0%
Duodenal	Number	3	2	5
	Valid % type PA	3,8%	5,0%	4,2%
Other	Number	17	7	24
	Valid % type PA	21,3%	17,5%	20,0%
Total	Number	80	40	120
	Valid % type PA	100,0%	100,0%	100,0%

Table 4.1.12. Allocation of patients according to the structure of the pancreatic parenchyma

Structure of the parenhyma		Type of PA		Total
		PJA-EXT DRAIN	PGA-MIX DRAIN	
soft	Number	32	14	46
	Valid % type PA	40,0%	35,0%	38,3%
hard	Number	48	26	74
	Valid % type PA	60,0%	65,0%	61,7%
Total	Number	80	40	120
	Valid % type PA	100,0%	100,0%	100,0%

Allocation of patients according to the initial localization of the adenocarcinoma and the structure of the pancreatic parenchyma in the two types of PA – PJA-EXT DRAIN and PGA-MIX DRAIN is compared in figure 4.1.2.



Head Ampullar Pr. Uncinatus Duodenal Other Soft parenchyma

Fig. 4.1.2. Frequency of the initial tumor localization and of the soft pancreatic parenchyma in PJA-EXT DRAIN and PGA-MIX DRAIN
PJA-EXT DRAIN (blue), PGA-MIX DRAIN (red)

Table 4.1.13. Allocation of patients according to the TNM stage of the tumor

TNM stage		Type of PA		Total
		PJA-EXT DRAIN	PGA-MIX DRAIN	
T1N0M0	Number	15	8	23
	Valid % type PA	18,8%	20,0%	19,2%
T2N0M0	Number	65	32	97
	Valid % type PA	81,3%	80,0%	80,8%
Total	Number	80	40	120
	Valid % type PA	100,0%	100,0%	100,0%

Table 4.1.14. Allocation of patients according to the degree of tumor differentiation G

Tumor differentiation		Type of PA		Total
		PJA-EXT DRAIN	PGA-MIX DRAIN	
G1	Number	5	2	7
	Valid % type PA	6,3%	5,0%	5,8%
G2	Number	54	26	80
	Valid % type PA	67,5%	65,0%	66,7%
G3	Number	17	8	25
	Valid % type PA	21,3%	20,0%	20,8%
G4	Number	4	4	8
	Valid % type PA	5,0%	10,0%	6,7%
Total	Number	80	40	120
	Valid % type PA	100,0%	100,0%	100,0%

Allocation of patients according to the TNM stage of the tumor and the degree of tumor differentiation G in the two types of PA – PJA-EXT DRAIN and PGA-MIX DRAIN is illustrated in figure 4.1.3.

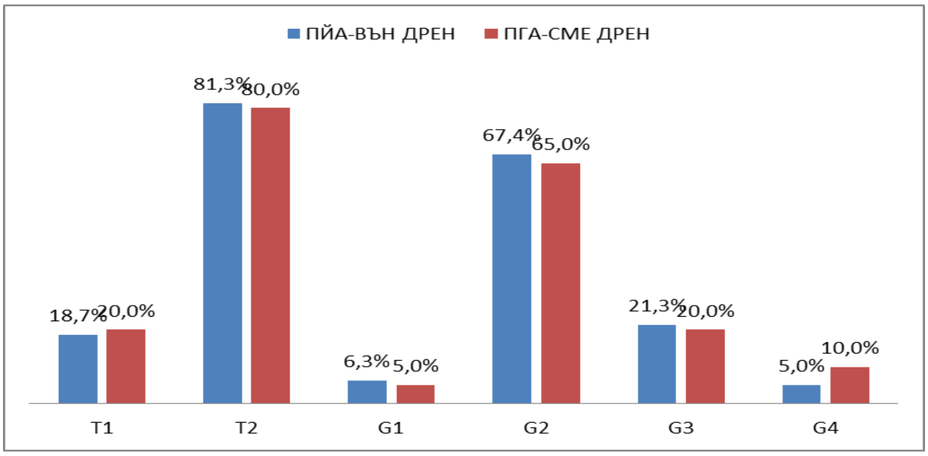


Fig. 4.1.3. Frequency of TNM stage and the degree of tumor differentiation in PJA-EXT DRAIN and PGA-MIX DRAIN PJA-EXT DRAIN (blue), PGA-MIX DRAIN (red)

4.2. Main clinical characteristics of the operated groups of patients

The results from the analysis of the frequency, the relative share and the relative risk of early postoperative complications (till the end of the first month) in patients are systematized in tables 4.2.1 – 4.2.20.

Allocation of patients according to the frequency of the insufficiency of pancreatic anastomosis (Insuf PA) can be seen in table 4.2.1.

Table 4.2.1. Allocation of patients according to the frequency of Insuf PA

Type of PA		Insuf PA		Total
		with	without	
PJA-EXT DRAIN	Number	23	57	80
	% Type of PA	28,8%	71,3%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% Type of PA	2,5%	97,5%	100,0%
Total	Number	24	96	120
	% Type of PA	20,0%	80,0%	100,0%

Table 4.2.2. shows the statistical significance of Insuf PA according to the Pearson χ^2 test.

Table 4.2.2. The statistical significance of Insuf PA according to the Pearson χ2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson χ2 test	11,484	0,001		
Correction of continuity	9,902	0,002		
Probability coefficient	14,760	0,000		
Fisher test		0,001		0,000
Linear association	11,389		0,000	
Number of valid cases	120			

The relative risk for occurrence of Insuf PA is shown in table 4.2.3.

Table 4.2.3. Relative risk for occurrence of Insuf PA

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/PGA-MIX DRAIN	15,737	2,040	121,405
For cohort with Insuf PA	11,500	1,610	82,118
For cohort without Insuf PA	0,731	0,630	0,847
Number of valid cases	120		

Allocation of patients according to the frequency of the clinically relevant PF "B+C" is shown in table 4.2.4.

Table 4.2.4. Allocation of patients according to the frequency of clinically relevant PF

Type of PA		PF "B+C"		Total
		with	without	
PJA-EXT DRAIN	Number	15	65	80
	% Type of PA	18,7%	81,3%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% Type of PA	2,5%	97,5%	100,0%
Total	Number	15	105	120
	% Type of PA	12,5%	87,5%	100,0%

Table 4.2.5 shows the statistical significance of the clinically significant PF „B+C" according to the Pearson χ^2 test, while table 4.2.6 – the relative risk for its occurrence.

Table 4.2.5. The statistical significance of the clinically significant PF „B+C" according to the Pearson χ2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson χ2 test	8,571	0,003		
Correction of continuity	6,943	0,008		
Probability coefficient	13,212	0,002		
Fisher test				0,001
Linear association	8,500	0,004	0,002	
Number of valid cases	120			

Table 4.2.6. Relative risk for occurrence of clinically significant PF

Relative risk	Value	95% confidence interval	
		Minimal	Maximal
For cohort without PF „B+C"	0,813	0,731	0,903
Number of valid cases	120		

Allocation of patients according to the frequency of IAH is shown in table 4.2.7.

Table 4.2.7. Allocation of patients according to the frequency of IAH

Type of PA		IAH		Total
		with	without	
PJA-EXT DRAIN	Number	14	66	80
	% Type of PA	17,5%	82,5%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% Type of PA	2,5%	97,5%	100,0%
Total	Number	15	105	120
	% Type of PA	12,5%	87,5%	100,0%

The statistical significance of IAH according to the Pearson χ^2 test and the relative risk for its occurrence are shown in table 4.2.8 and table 4.2.9.

Table 4.2.8. Statistical relevance of IAH according to the Pearson $\chi 2$ test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson $\chi 2$ test	5,486	0,019		
Correction of continuity	4,200	0,040		
Probability coefficient	6,876	0,009		
Fisher test			0,019	0,014
Linear association	5,440	0,020		
Number of valid cases	120			

Table 4.2.9. Relative risk for occurrence of IAH

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN / PGA-MIX DRAIN	8,273	1,047	65,365
For cohort with IAH	7,000	0,954	51,359
For cohort without IAH	,846	0,756	0,947
Number of valid cases	120		

The allocation of patients according to the frequency of IAI is shown in table 4.2.10.

Table 4.2.10. Allocation of patients according to the frequency of IAI

Type of PA		IAI		Total
		with	without	
PJA-EXT DRAIN	Number	15	65	80
	% cin Type of PA	18,7%	81,3%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% cin Type of PA	2,5%	97,5%	100,0%
Total	Number	16	104	120
	% cin Type of PA	13,3%	86,7%	100,0%

The statistical significance of IAI according to the Pearson χ^2 test and the relative risk for its occurrence are shown in table 4.2.11 and table 4.2.12.

Table 4.2.11. Statistical significance of IAI according to the Pearson χ2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson χ2 test	6,094	0,014		
Correction of continuity	4,769	0,029		
Probability coefficient	7,677	0,006		
Fisher test			0,020	0,009
Linear association	6,043	0,014		
Number of valid cases	120			

Table 4.2.12. Relative risk for occurrence of IAI

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/ PGA-MIX DRAIN	9,000	1,144	70,812
For cohort with IAI	7,500	1,027	54,776
For cohort without IAI	0,833	0,742	0,936
Number of valid cases	120		

Allocation of patients according to the frequency of gastroparesis and DSE is shown in table 4.2.13.

Table 4.2.13. Allocation of patients according to the frequency of gastroparesis and DSE

Type of PA		Gastroparesis and DSE		Total
		with	without	
PJA-EXT DRAIN	Number	14	66	80
	% Type of PA	17,5%	82,5%	100,0%
PGA-MIX DRAIN	Number	2	38	40
	% Type of PA	5,0%	95,0%	100,0%
Total	Number	16	104	120
	% Type of PA	13,3%	86,7%	100,0%

The statistical significance of gastroparesis and DSE according to the Pearson χ^2 test and the relative risk for their occurrence are shown in table 4.2.14 and table 4.2.15.

Table 4.2.14. Statistical significance of gastroparesis and DSE according to the Pearson χ2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson χ2 test	3,606	0,058		
Correction of continuity	2,605	0,107		
Probability coefficient	4,164	0,041		
Fisher test			0,086	0,047
Linear association	3,576	0,059		
Number of valid cases	120			

Table 4.2.15. Relative risk for the occurrence of gastroparesis and DSE

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/ PGA-MIX DRAIN	4,030	0,869	18,695
For cohort with gastroparesis and DSE	3,500	0,836	14,657
For cohort without gastroparesis and DSE	0,868	0,768	0,983
Number of valid cases	120		

Allocation of patients according to the frequency of WI can be seen in table 4.2.16.

Table 4.2.16. Allocation of patients according to the frequency of WI

Type of PA		WI		Total
		with	without	
PJA-EXT DRAIN	Number	12	68	80
	% Type of PA	15,0%	85,0%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% Type of PA	2,5%	97,5%	100,0%
Total	Number	13	107	120
	% Type of PA	10,8%	89,2%	100,0%

The statistical relevance of WI according to the Pearson χ^2 test and the relative risk for its occurrence are shown in table 4.2.17 and table 4.2.18.

Table 4.2.17. Statistical significance of WI according to the Pearson $\chi 2$ test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson $\chi 2$ test	4,313	0,038		
Correction of continuity	3,116	0,078		
Probability coefficient	5,338	0,021		
Fisher test			0,058	0,031
Linear association	4,277	0,039		
Number of valid cases	120			

Table 4.2.18. Relative risk for occurrence of WI

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/ PGA-MIX DRAIN	6,882	0,862	54,960
For cohort with WI	6,000	0,808	44,529
For cohort without WI	0,872	0,785	0,968
Number of valid cases	120		

Allocation of patients according to the frequency of BL is shown in table 4.2.19.

Table 4.2.19. Allocation of patients according to the frequency of BL

Type of PA		BL		Total
		with	without	
PJA-EXT DRAIN	Number	11	69	80
	% Type of PA	13,8%	86,3%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% Type of PA	2,5%	97,5%	100,0%
Total	Number	12	108	120
	% Type of PA	10,0%	90,0%	100,0%

Tables 4.2.20 and 4.2.21 show the statistical relevance of WI according to the Pearson χ^2 test and the relative risk for its occurrence

Table 4.2.20. Statistical relevance of BL according to the Pearson χ2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson χ2 test	3,750	0,053		
Correction of continuity	2,604	0,107		
Probability coefficient	4,603	0,032		
Fisher test			0,059	0,045
Linear association	3,719	0,054		
Number of valid cases	120			

Table 4.2.21. Relative risk for occurrence of BL

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/ PGA-MIX DRAIN	6,217	0,773	49,988
For cohort with BL	5,500	0,736	41,115
For cohort without BL	0,885	0,800	0,978
Number of valid cases	120		

The total one-month postoperative morbidity of patients according to the type of PA can be seen in table 4.2.22, the statistical significance of this morbidity according to the Pearson χ^2 test – in table 4.2.23, while the relative risk for its occurrence – in table 4.2.24.

Table 4.2.22. One-month postoperative morbidity of patients according to the type of PA

Type of PA		Morbidity		Total
		with	without	
PJA-EXT DRAIN	Number	38	42	80
	% Type of PA	47,5%	52,5%	100,0%
PGA-MIX DRAIN	Number	3	37	40
	% Type of PA	7,5%	92,5%	100,0%
Total	Number	41	79	120
	% Type of PA	34,2%	65,8%	100,0%

Table 4.2.23. Statistical significance of one-month postoperative morbidity according to the Pearson χ2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson χ2 test	18,969	0,000		
Correction of continuity	17,232	0,000		
Probability coefficient	22,098	0,000		
Fisher test			0,000	0,000
Linear association	18,811	0,000		
Number of valid cases	120			

Table 4.2.24. Relative risk for one-month postoperative morbidity

Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/ PGA-MIX DRAIN	11,159	3,179	39,172
Cohort morbidity with morbidity	6,333	2,082	19,265
Cohort morbidity without morbidity	0,568	0,453	0,712
Number of valid cases	120		

Total one-month mortality of patients according to the type of PA can be seen in table 4.2.25, the relative share of postoperative complications according to the type of PA based on literary data - in table 4.2.26, the statistical significance of this mortality according to the Pearson χ^2 test – in table 4.2.27, while the relative risk for its occurrence – in table 4.2.28.

Table 4.2.25. Total one-month mortality of patients according to the type of PA

Type of PA		Total mortality		Total
		with	without	
PJA-EXT DRAIN	Number	12	68	80
	% Type of PA	15,0%	85,0%	100,0%
PGA-MIX DRAIN	Number	1	39	40
	% Type of PA	2,5%	97,5%	100,0%
Total	Number	13	107	120
	% Type of PA	10,8%	89,2%	100,0%

Table 4.2.6. Average frequency of postoperative complications according to the type of PA based on literary data (in %)

Type of PA	PF	DSE	IAI	IAH	WI	**BL**	Morb.	Mort.	Revision
PJA	20,0	13,0	9,0	10,0	10,0	5,0	49,0	4,0	11,0
PGA	13,0	16,0	8,0	9,0	6,0	3,0	48,0	4,0	10,8
PA average	16,5	14,5	8,5	9,5	8,0	4,0	48,5	4,0	10,5

PGA has a definite advantage over PJA as regards the frequency of PF and weaker – as regards WI, but it is linked to an enhanced risk for DSE. The two surgical procedures are equal as regards the remaining indicators (table 4.2.6).

Table 4.2.27. Statistical relevance of the total one-month mortality according to the Pearson χ^2 test

Indicator	Value	Level of relevance (bilateral, asymptomatic)	Level of relevance (bilateral, exact)	Level of relevance (unilateral, exact)
Pearson $\chi 2$ test	4,313	0,038		
Correction of continuity	3,116	0,078		
Probability coefficient	5,338	0,021		
Fisher test			0,058	0,031
Linear association	4,277	0,039		
Number of valid cases	120			

Table 4.2.28. Relative risk for total one-month mortality

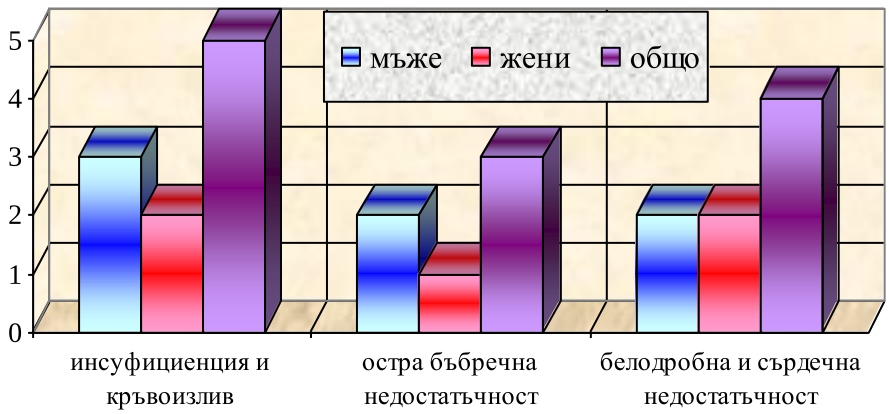
Relative risk/Type of PA	Value	95% confidence interval	
		Minimal	Maximal
PJA-EXT DRAIN/ PGA-MIX DRAIN	6,882	0,862	54,960
For cohort with mortality	6,000	0,808	44,529
For cohort without mortality	0,872	0,785	0,968
Number of valid cases	120		

Fig. 4.2.1 shows our own results as regards the causes for death in PJA-EXT DRAIN, while fig. 4.2.2 – the one-month morbidity and mortality in operated patients, subjected to PJA-EXT DRAIN and PGA-MIX DRAIN. In fig. 4.2.3 these data have been compared with the results from the survey of foreign literature in the use of PJA and PGA, while in fig. 4.2.4 – the relative share of early postoperative complications in PJA-EXT DRAIN and PGA-MIX DRAIN in our patients has been compared to this in PJA and PGA based on literary data. Following the application of PGA-MIX DRAIN only one male patient passed away due to insufficiency and hemorrhage.

Apparently better results in terms of morbidity and mortality rates have been achieved in the course of our research.

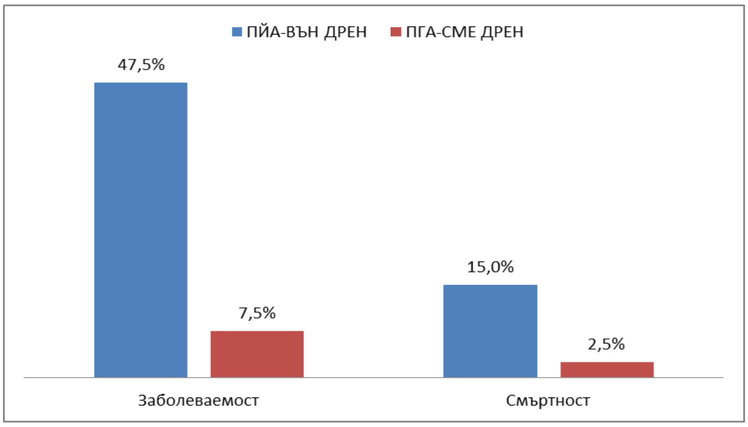
The relative share of early postoperative complications in our patients with PJA-EXT DRAIN is higher as compared to averaged results from accessible research by foreign authors on PJA. The relative share of early postoperative complications in our patients with PGA-MIX DRAIN is lower as compared to averaged results from accessible research by foreign authors on PGA. Application of the surgical procedure of PJA-EXT DRAIN is linked to lower efficiency as compared to the weighted surgical results by other authors. The application of the new surgical procedure PGA-MIX DRAIN is linked to higher efficiency as compared to the averaged surgical results obtained by other authors (fig. 4.2.4).

Men women total



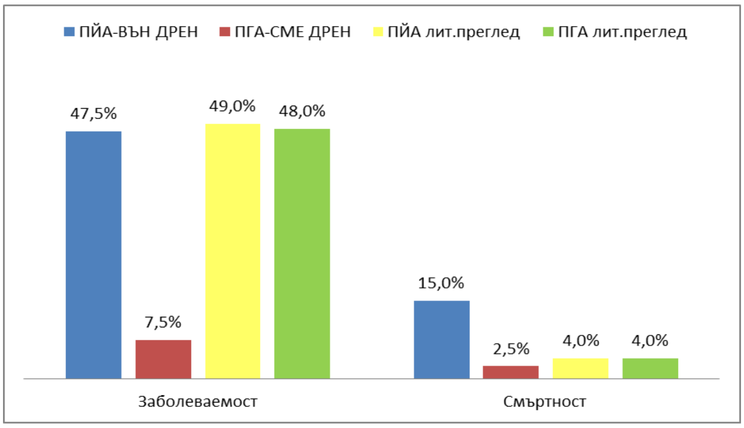
Insufficiency and hemorrhage *Acute kidney injury* *Respiratory and heart failure*

Fig 4.2.1. Causes for death in male and female patients with PJA-EXT DRAIN



Morbidity Mortality

Fig 4.2.2. One-month postoperative morbidity and mortality rates in PJA-EXT DRAIN and PGA-MIX DRAIN



Morbidity Mortality

Fig 4.2.3. One-month post-operative morbidity and mortality rates in PJA-EXT DRAIN and PGA-MIX DRAIN in our patients and in PJA and PGA based on literary data

PJA-EXT DRAIN PGA-MIX DRAIN PJA literary survey PGA literary survey
Morbidity Mortality

PJA-EXT DRAIN PGA-MIX DRAIN PJA PGA

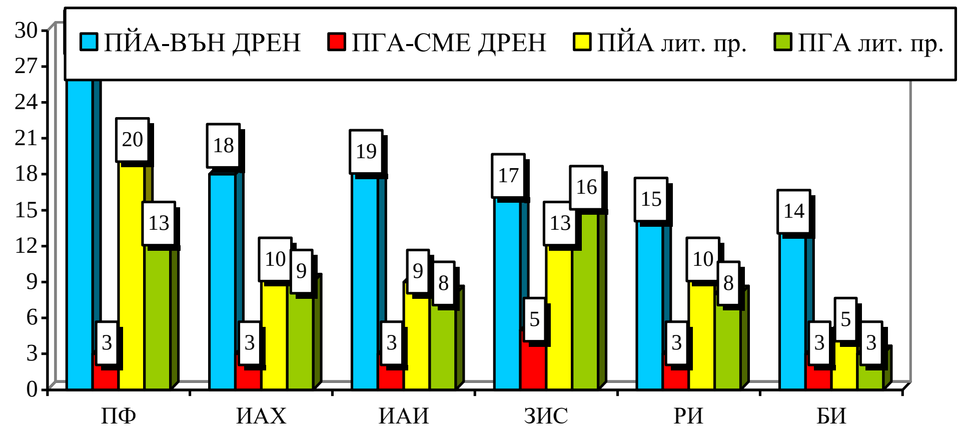


Fig 4.2.4. Relative share of early postoperative complications in PJA-EXT DRAIN and PGA-MIX DRAIN in our patients and in PJA and PGA based on literary data
PJA-EXT DRAIN PGA-MIX DRAIN PJA literary survey PGA literary survey

The allocation of weighted average values of hospitalization according to the type of PA is shown in table 4.2.29.

Table 4.2.29. Allocation of weighted average values of hospitalization

Hospitalization/Type of PA	Huber	Tukey	Hampel's	Andrew
PJA-EXT DRAIN	20,68	20,50	21,44	20,48
PGA-MIX DRAIN	9,59	9,26	9,42	9,26

One-month mortality, morbidity and early postoperative complications according to the type of PA have been systematized in table 4.2.30.

Table 4.2.30. Mortality, morbidity and early postoperative complications in two groups of patients with PDR

Variable	PJA-EXT DRAIN n (%) (n=80)	PGA-MIX DRAIN n (%) (n=40)	OR	p
Mortality within a month	12 (15.0%)	1 (2.5%)	6,8	[1]0,058
Morbidity	38 (47.5%)	3 (7.5%)	11,2	[1]0,000
PF	23 (28.8%)	1 (2.5%)	15,7	[1]0,000
PF („B“ + „C“)	15 (18.8%)	1 (2.5%)	9,0	[1]0,020
IAH	14 (17.5%)	1 (2.5%)	8,2	[1]0,019
IAI	15 (18.8%)	1 (2.5%)	9,0	[1]0,020
DSE	14 (17.5%)	2 (5.0%)	4,0	[1]0,086
WI	12 (15.0%)	1 (2.5%)	6,9	[1]0,058
BL	11 (13.8%)	1 (2.5%)	9,0	[1]0,059
Hospitalization (days)	22	11		[2]0,000

OR – odds ration, [1]Fisher criterion, [2]Mann-Whitney test

5. DISCUSSION

5.1. Preoperative characteristics of the studied groups of patients

The two groups have been randomized according to the main epidemiological characteristics of the patients (sex, age, clinic symptomatic, initial tumor localization, stage of the tumor growth, stage of tumor differentiation G and structure of the pancreatic parenchyma) and differ only in the type of the implemented surgical procedure. The two procedures have equal sequence and volume of PDR, but differ in the reconstruction of digestive anastomoses and the way of their drainage. Preoperatively for therapeutic purpose ERCPG was carried out, since the diameter of the common bile duct is a risk factor for the occurrence of PF. The dependence of the complications on the structure of the pancreatic parenchyma and the diameter of the common pancreatic duct (wide – over 3.00 mm and narrow under 3.00 mm) has been proven in plenty of research (38, 68, 149).

The risk assessment with regard to PF of the international research group (FRSG, Fistula Risk Score Group) includes four high-risk factors: soft texture of the gland parenchyma, diameter of the pancreatic duct <3.0÷4.0 mm, cyst pathology (lack of fibrosis or fat dystrophy) and intraoperative hemorrhage (>1000÷1500 mL) (43).

Significant risk factors for PF are linked to the pancreas (normal and soft texture of the gland parenchyma, diameter of the pancreatic duct <3.0÷4.0 mm, adenocarcinomas with duodenal and ampullar localization and cyst pathology), with patient – male, age over 70 years (68), cerebro-vascular disease and duration of jaundice (149) and with the surgical procedure – intraoperative hemorrhage >1000÷1500 mL, blood transfusion >500 mL, type PJA of the anastomosis and the experience of the surgeon – less than 4-5 PDR per year.

Our patients are not randomized according to the volume of intraoperative hemorrhage due to insufficiently precise data in the medical documentation.

The lower value of the creatinine clearance (<50 mL/min) is a risk factor for PF, since it is linked to the development of acute kidney injury, IAH and IAI, enhancing the risk for this complication. We have established jaundice statistically correctly more often in PGA-MIX DRAIN than in PJA-EXT DRAIN (p=0,027). The occurrence of jaundice does not correlate with the severity of the disease, no significant difference being established between the two groups of patients as regards ERCPG results (p>0,05).

The differences between the two groups in terms of other clinical symptoms (epigastric pain, weight loss, nausea and vomiting, gastrointestinal bleeding – haemathemesis and melena and sugar diabetes) are also statistically unreliable (p>0.05).

Duodenal and ampullar adenocarcinomas (156) and the soft gland parenchyma (38,68) are independent risk factors for PF. Allocation of patients in the two studied groups as regards both the initial tumor localization and the structure of the pancreatic parenchyma, as well as the TNM stage and the degree of tumor differentiation is approximately the same ($p>0,05$).

A summary can be made that there is an approximately equal preoperative structure of the patients, subjected to these two operative interventions, which is a prerequisite for the correctness of the subsequent analysis.

5.2. Postoperative results from the application of PGA-MIX DRAIN and PJA-EXT DRAIN

The frequency of postoperative complications, the relative risk for their occurrence and the duration of hospitalization characterize the degree of efficiency of the operational intervention. Apart from the total mortality (up to 50%) and morbidity (35.0%-60.0%) these indicators are further supplemented by the cases of reoperation (up to 100%) and related systemic complications (122). Reoperations and systemic complications are direct consequence from early postoperative complications. It is wrong to report them independently as initial measurement of the efficiency of the surgical procedure. Revision due to these early complications is necessitated in 10% of the operated patients. The most common systemic complications are pulmonary (in 9.9%, namely – pneumonia (in 5%), pleural effusion (in 3%), respiratory failure (in 2.0%), pleural empyema (in 0.5%) and pulmonary embolism (in 0.5% of the cases) (152).

In our cohort research we compared the frequency of early postoperative complications in patients subjected to the risk factor – type of surgical intervention PJA-EXT DRAIN against PGA-MIX DRAIN and estimates the relative risk in both groups of patients.

Both our own results and data from available literature show that PGA has a definite advantage over PGA as regards the frequency of PF, but it is linked to higher risk for more frequent DSE. The two surgical procedures are equal as regards both the remaining early postoperative complications and the total one-month postoperative morbidity and mortality, the number of reoperations and the duration of hospitalization.

The relative share of early postoperative complications in our patients with PJA-EXT DRAIN is higher as compared to the average results from available research by other foreign authors on PJA. The relative share of early postoperative complications in our patients with PGA-MIX DRAIN is lower than the average results from available research by foreign authors on PGA (44,115,122,144,202 and other). Applying the surgical procedure PJA-EXT DRAIN in our patients is linked to lower efficiency than the one of average surgical results, obtained by other authors (76,145 and other). Applying the new surgical procedure PGA-MIX DRAIN in our patients is linked to higher efficiency than the one of average surgical results, obtained by other authors (62,122,202 and other).

The results from the correlation analysis with the Pearson χ^2 test in our patients show the existence of a statistically relevant causal link between the type of surgical procedure (PJA-EXT DRAIN or PGA-MIX DRAIN), on the one hand and the occurrence of Insuf PA, on the other hand ($p<0,05$). According to Cramer's correlation coefficient this link is of average degree – 0.4. This means that the type of surgical procedure has a certain impact, but it is not decisive for the occurrence of Insuf PA. In patients with Insuf PA following treatment by means of PJA-EXT DRAIN a frequency of this complication of 28.8% has been established, and following treatment by means of PGA-MIX DRAIN – only 2.5%, i.e. it is 11.52 times bigger. PJA-EXT DRAIN is a risk factor for the occurrence of Insuf PA and is linked to 15.737 times higher risk of this complication (odds ratio of 15.737; between 2.040 and 121.405 at 95% confidence interval)

While in patients treated by us with PJA-EXT DRAIN a frequency of PF "B+C" of 18.8% has been established, its average in the application of PJA by foreign authors is slightly lower (16.0%). It is worth noting that in our patients treated with PGA-MIX DRAIN, this complication is lacking entirely. These results show that we achieved maximally high clinical efficiency of the optimized surgical procedure.

The relative share of PF is reported to be most often in the range 9.0%÷14.0% (103). We have established a relative share of PF for PJA-EXT DRAIN of 28.8%. It is higher than the average values in the publications of foreign authors, which fall within a range of 20.0%. This is attributable to the lower clinical efficiency of this surgical procedure in our patients. On the other hand, the relative share of PF in patients, subjected to PGA-MIX DRAIN is only 2.5%. It is 5.2 times lower than its average for PGA, reported by foreign authors (13.0%). This is a convincing proof of the higher clinical efficiency achieved by us in the optimized surgical procedure.

The results from the correlation analysis with the Pearson χ^2 test in our patients show the existence of a statistically relevant causal link between the type of surgical procedure (PJA-EXT DRAIN or PGA-MIX DRAIN) on the one hand and the occurrence of IAH, on the other hand ($p<0,05$). According to Cramer's correlation coefficient this link is of weaker grade – 0.2. Therefore the type of surgical procedure has a certain impact, but it is not decisive for the occurrence of IAH. In patients with IAH following treatment by means of PJA-EXT DRAIN a relative share of this complication of 17.5% is established, and following treatment by means of PGA-MIX DRAIN – only 2.5%, i.e. in the first group it is 7.0 times higher. PJA-EXT DRAIN is a risk factor for the occurrence of IAH and it is linked to 8.273 higher risk for this complication (odds ratio of 8.273; between 1.047 and 65.365 at 95% confidence interval).

A value of 7.1% (152) and of 17.5% (7) is reported for the relative share of IAH. Average values of IAH in PJA according to data by foreign authors fall within the range of 10.0%. This shows the lower clinical efficiency of PJA-EXT DRAIN applied by us. We have established by 3.6 times lower relative share of IAH following the application of PGA-MIX DRAIN as compared to average data by foreign authors for the use of PGA of 9.0%. This fact clearly testifies to higher clinical efficiency of the optimized surgical procedure used by us.

According to the results from the correlation analysis with the Pearson χ^2 test in our patients there is a statistically reliable causal link between the type of surgical procedure (PJA-EXT DRAIN or PGA-MIX DRAIN) on the one hand and the occurrence of IAI on the other hand ($p<0,05$). According to Cramer's correlation coefficient this link is of weak grade – 0.2, which means that the type of surgical procedure has a certain impact, but it is not a decisive factor for the occurrence of IAI. In patients with IAI following treatment by means of PJA-EXT DRAIN a relative share of 18.8% of this complication has been established, and following treatment by means of PGA-MIX DRAIN – only of 2.5%, i.e. it is 7.0 times higher in the first group. PJA-EXT DRAIN is a risk factor for the occurrence of IAI and is linked to 9.0 times higher risk for this complication (odds ratio of 9.000; between 1.144 and 70.812 at 95% confidence interval).

The relative share of IAI ranges between 17.0% (77) and 25.5% (158). In our patients we have established a bigger relative share of IAI as compared to its average value of 9.0% according to foreign publications. Therefore, our research shows a lower clinical efficiency of the applied surgical procedure. On the other hand, the relative share of IAI in the application of PGA-MIX DRAIN in our patients is 3.2 times lower than the average values of foreign authors as regards PGA of 9.0%. This convincingly proves the higher clinical efficiency of this optimized surgical procedure used by us.

In the correlation analysis with the Pearson χ^2 test in our patients a statistically reliable causal link has been identified between the type of surgical procedure (PJA-EXT DRAIN and PGA-MIX DRAIN) on the one hand and the occurrence of gastroparesis and DSE on the other hand ($p<0,05$). According to Cramer's correlation analysis this link is of weaker degree - 0.2. This shows that the type of surgical procedure has a weak impact and it is not a decisive factor for the occurrence of gastroparesis and DSE. In patients with gastroparesis and DSE following treatment by means of PJA-EXT DRAIN a relative share of this complication of 17.5% has been established, while following treatment by means of PGA-MIX DRAIN – of 5.0%, i.e. in the first group it is by 3.5 times higher. PJA-EXT DRAIN is a risk factor for the occurrence of this serious complication and is linked to 4.030 times higher risk for it (odds ratio of 4.030; between 0.869 and 18.695 at a 95% confidence interval).

DSE comprises a frequent early postoperative complication and is observed in 8.0%-45% of cases (52). The relative share of gastroparesis and DSE in our patients, subjected to PJA-EXT DRAIN is slightly higher than the average relative share according to data by foreign authors of 13%. It obviously speaks of similar clinical efficiency of the two surgical procedures. The relative share of gastroparesis and DSE in our patients, subjected to PGA-MIX DRAIN is by 3.2 times lower than the average relative share according to data by foreign authors about PGA of 16.0%. This is attributable to the higher clinical efficiency of this optimized surgical procedure achieved by us.

The correlation analysis with the Pearson χ^2 test conducted in our patients established a statistically relevant causal link between the type of surgical procedure

(PJA-EXT DRAIN or PGA_MIX DRAIN) on the one hand and the occurrence of WI, on the other hand ($p<0,05$). According to Cramer's correlation coefficient this link is of weaker degree – 0.2. For this reason the type of surgical procedure has an insignificant impact and is not a decisive factor for the occurrence of WI. In patients with WI following treatment by means of PJA-EXT DRAIN a relative share of this complication of 15.0% has been established, and following the application of PGA-MIX DRAIN – of 2.5%, i.e. in the first group it is by six times higher. PJA-EXT DRAIN is a risk factor for the occurrence of this serious complication and is linked to 6.882 times higher risk for it (odds ratio of 6.882; between 0.862 and 54.960 at 95% confidence interval).

A frequency of WI of 2.0% (160) and of 15.0% (42) has been established. Since the relative share of WI in our patients, subjected to PJA-EXT DRAIN is higher than the average relative share, reported by foreign authors on PJA of 10%, our clinical efficiency of this surgical procedure is lower.

The relative share of WI in our patients, subjected to PGA-MIX DRAIN is by 2.4 times lower than the average relative share according to data by foreign authors about PGA of 6.0%. This is due to the higher clinical efficiency of our optimized surgical procedure.

The results from the correlation analysis with the Pearson χ^2 test in our patients testify to the existence of a statistically reliable causal link between the type of surgical procedure (PJA-EXT DRAIN or PGA-MIX DRAIN), on the one hand and the occurrence of BL, on the other hand ($p<0,05$). According to Cramer's correlation coefficient this link is of weaker degree – 0.2. Therefore the type of surgical procedure has a certain impact but it is not a decisive factor for the occurrence of BL. In patients with BL following treatment with the help of PJA-EXT DRAIN a relative share of this complication of 13.8% is observed and following treatment by means of PGA-MIX DRAIN – only 2.5%. This relative share is by 5.52 times higher in the first than in the second group. PJA-EXT DRAIN is a risk factor for the occurrence of BL and is linked to 6.217 times higher risk for it (odds ratio of 6.217; between 0.773 and 49.988 at 95% confidence interval).

The frequency of BL varies between 7.6% (63) and 12.1% (60).

Since the relative share of BL in our patients, subjected to PJA-EXT DRAIN is higher than the average relative share, reported by foreign authors on PJA of 5.0%, the conclusion can be drawn that our clinical efficiency as regards this surgical procedure is lower.

The relative share of BL in the use of PGA-MIX DRAIN is closer to the average relative share according to data of foreign authors about PGA of 3.0%.

Insufficiency of HJA with bile leak into the abdominal cavity and the development of IAI under the form of biliary peritonitis and necrosis of the pancreatic stump are observed more rarely – in 5.0-8.0% of cases (158).

With the help of the correlation analysis with the Pearson χ^2 test we have established a statistically reliable causal link between the type of surgical procedure (PJA-EXT DRAIN and PGA-MIX DRAIN), on the one hand and the occurrence of early post-operative complications, on the other hand ($p<0,05$). According to the results from the research of Cramer's correlation coefficient this link is of medium degree – 0.4. There is a certain impact of the type of surgical procedure, but it is not a decisive factor for the occurrence of early postoperative complications. The relative share of our patients with early postoperative complications, treated with PJA-EXT DRAIN (of 47.5%) is by 6.33 times higher than that of patients with such complications, treated with PGA-MIX DRAIN (of 7.5%). The relative share of our patients with one-month postoperative morbidity in the use of PGA-MIX DRAIN is by 6.4 times lower in terms of early postoperative complications as compared to average relative share according to data by foreign authors about PGA of 48.0%. This is related to the higher clinical efficiency of the surgical procedure optimized by us. PJA-EXT DRAIN is a risk factor for the occurrence of early postoperative complications and is linked to 11.159 times higher risk for them (odds ratio of 11.159; between 3.179 and 39.172 at 95% confidence ritual).

The total early postoperative morbidity varies between 30.0% and 60.0% (30.39 and other) at an average value of 49.0% as regards PJA in publications by foreign authors. Therefore, it can be concluded that the clinical efficiency of the surgical procedures applied by us is equal to that of foreign authors.

The results from the correlation analysis with the Pearson χ^2 test in our patients testify to the existence of a statistically reliable causal link between the type of surgical procedure (PJA-EXT DRAIN or PGA-MIX DRAIN), on the one hand and the occurrence of death, on the other hand ($p<0,05$). According to Cramer's correlation coefficient this link is of weak degree – 0.2. This shows that the type of surgical procedure has a certain impact, but it is not a decisive factor for the occurrence of death. The relative share of patients who die after treatment with PJA-EXT DRAIN (of 15.0%) is six times higher than this of patients who die after treatment with PGA-MIX DRAIN (of 2.5%). PJA-EXT DRAIN is a risk factor for one-month mortality after treatment and is linked to 6.882 times higher risk for them (odds ratio of 6.882; between 0.862 and 54.960 at a 95% confidence interval).

Total early perioperative mortality, published in accessible literature ranges between 3.0%-5.0% at an average result of 4.0% as regards PJA. The relative share of deaths in our contingent following treatment with PJA-EXT DRAIN is 3.75 times higher, which is linked to lower clinical efficiency of the applied surgical procedure. On the other hand, the relative share of our death cases following treatment with PGA-MIX DRAIN is 1.6 times lower than the average result of 4.0% as regards PGA. This testifies to a higher clinical efficiency of the surgical procedure optimized by us.

The average duration of hospitalization in our patients, subjected to PJA-EXT DRAIN is twice higher than in those, subjected to PGA-MIX DRAIN (22 against 11 days). According to the results from Mann-Whitney's non-parametric test, the difference between these two average values is statistically reliable ($Z=-7,399$; $p<0.0001$).

The question about the exact time for removing the drains is also of some interest.

Stent placement through PDA after PDR can be useful for diverting the pancreatic juice from the place of anastomosis, the decompressing of the remaining pancreas and the maintenance of passability of the common pancreatic duct. Nevertheless, the benefits remain controversial. The complications with the external stent are linked to the moment of removing it, while with the internal one – with the high frequency of atypical migration. The external and internal stent show comparable clinical results in the short-term and long-term, the type of pancreatic stent being a subjective choice of the surgeon (46). The use of external stents can be linked to the significant decrease in the frequency of PF (14.0%-16.0%), the frequency of significant postoperative complications (intra-abdominal abscess, IAA, DSE and WI by 8.0%-9.0%) and the continuation of hospitalization (by 20 days) (46). The use of external stent in patients with soft gland parenchyma and narrow pancreatic duct (<3.0 mm) is linked to higher risk for PF (35.0%-37.0%) and postoperative morbidity (46,0%-60,0%) (201), while the benefits from its use as compared to its rejection are controversial (46.201).

The time for removing the drain is an independent risk factor for PF. The early removal of drains on the third or fourth day is linked to lower frequency of PF, abdominal and pulmonary complications, while the average hospitalization is shorter. Removing drains up to the 72^{nd} hour is recommended for patients with low risk for occurrence of PF (hard parenchyma, pancreatic duct with width >3.0 mm and contents of amylase in the drain up to 5000 U/L) (111).

The more continuous keeping of drains makes sense in patients with higher risk for PF (soft parenchyma, pancreatic duct with width <3.0 mm and contents of amylase in the drains over 5000 U/L). Persisting drains for over three weeks is an independent risk factor for the occurrence of PF (113).

6. CONCLUSION

On the basis of the multi-aspect research conducted by us, the following **conclusions** can be drawn:

1. The lack of postoperative resective stumps, the construction of one-loop digestive anastomoses and their mixed (internal and external) intraluminal drainage by active and passive aspiration brings about a series of positive results:

1-a. A significant decrease in the relative share of the one-month total morbidity in patients, subjected to PGA-MIX DRAIN – up to 7.5%.

1-b. A significant decrease in the relative share of early postoperative complications in patients, subjected to PGA-MIX DRAIN, as follows: of Insuf PA, IAH, WI and BL – up to 2.5%, of gastroparesis and DSE – up to 5.0%, and of clinically relevant PF – up to 2.5%.

1-c. Significant decrease in the relative share of the one-month morbidity in patients subjected to PGA-MIX DRAIN – up to 2.5%.

2. In patients, subjected to PJA-EXT DRAIN there is 10 times higher risk on the average for the occurrence of significant early postoperative complications.

3. The average hospitalization of patients, subjected to PGA-MIX DRAIN is twice shorter than that of patients, treated with PJA-EXT DRAIN.

7. LIST OF PUBLICATIONS, RELATED TO THE DISSERTATION

1. **Mena N,** Glinkov S, Kirov K. Pancreaticodigestive anastomosis optimization in pancreaticoduodenal resection patients. *Medicus*, 2019;24(3):294-302.
2. **Mena N,** Marinova-Kichikov PG, Kirov KG. Optimized drainage of pancreatic-digestive anastomosis in patients with pancreatoduodenal resection. *J Biomed Clin Res*., 2022;15(2):135-141.
3. Kirov KG, **Mena N.** Our experience with multivisceral resections for locally advanced colorectal cancer. *IOSR J Dent Med Sci.*, 2021;20(11):63-68.

8. CONTRIBUTIONS OF THE DISSERTATION

The contributions of the dissertation are of both scientific-applied and original and affirmative character.

Contributions of scientific-applied and original character

1. For the first time a comprehensive approach is offered to reducing early postoperative complications in patients with PDR – optimized reconstruction and a new type (mixed) of joint drainage of three digestive anastomoses, leading to a significant recovery of the "horseshoe-shaped" anatomic configuration between the stomach and the intestine.

2. For the first time a new original mixed method is proposed for internal and external common intraluminal drainage of the three digestive anastomoses.

3. The comprehensive approach achieves a statistically relevant decrease in early postoperative complications to levels, corresponding to modern surgical treatment.

Contributions of affirmative character

1. The opinion has been confirmed that the reconstruction of one-loop digestive anastomoses is linked to reduction of early postoperative complications.

2. The opinion has been confirmed that the replacement of PJA with PGA and the stent placement in the common duct largely secures the functional integrity of PDA, which is a prerequisite for a better clinical effect.

3. The opinion has been confirmed that surgical principles for proper hemostasis, vitality and precise work, lack of tension in anastomoses and the correct placement of tissues, as well as the use of subtle material for stitching and the very surgical technique for different sutures ensure greater stability and functionality of the pancreatic anastomosis.