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PECULIARITIES OF THE EXOCRINE PANCREATIC FUNCTION AFTER DUODENOPANCREATIC RESECTION ON THE OCCASION OF ADENOCARCINOMA

A U T O R E F E R A T E

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TABLE OF CONTENT

USED ABBREVIATIONS

PA	pancreatic adenocarcinoma
PGA	pancreaticogastrostomy
PJ	pancreaticojejunostomy
PPPD	pylorus-preserving pancreaticoduodenectomy
PD	pancreaticoduodenectomy
PEI	pancreatic enzyme insufficiency
CT	computed tomography
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
FE-1	fecal elastase-1
ERCP	endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
ISGPS	International Study Group on Pancreatic Surgery
PPF	pancreatic fistula
DGE	delayed gastric emptying
PPH	post-pancreatectomy hemorrhage
VDR	vitamin D receptor
PERT	pancreatic enzyme replacement therapy
PS	performance status

1. INTRODUCTION

Pancreatic adenocarcinoma ranks fourth as a cause of death due to cancer, with survival being the last in comparison with other types of neoplasms, and has remained unchanged over the past 40 years [43]. The reason for the poor prognosis is the biology of the tumor, its late diagnosis and the lack of effective screening for the early detection of this type of neoplasm. Pancreatoduodenectomy is the only treatment approach providing potential cure in patients with pancreatic head adenocarcinoma. Despite the aggressive modern techniques for intervention on borderline resectable tumors infiltrating the arterial and venous main vessels, and the performance of radical tumor resection along the axis of the portal-superior mesenteric vein, celiac artery and mesenteric artery, after neoadjuvant chemotherapy, only ten percent of newly diagnosed patients with this pathology can be operated radically at the time of their diagnosis. Pancreatoduodenectomy as a multi-organ resection surgery in abdominal surgery is charged with an incidence rate of 18–52% [158, 198, 224, 229, 231, 256] and a mortality rate of less than 3% [48, 51, 115]. The combination of major surgical intervention and limited expected survival makes the quality of life factor extremely important for these patients. Postoperative complications are one of the leading reasons for the deterioration of this indicator after duodenopancreatic resection for neoplasms. Complications in percentage terms according to the available literature sources are as follows: post-pancreatectomy fistula (PPF) 3–45% [26, 27, 251, 257]; impaired gastric emptying (DGE) 17.3% [159]; post-pancreatectomy hemorrhage (PPH) 5–12% [198], with one of the leading causes of these complications being the choice of reconstructive technique. The technical feasibility of using pyloric pancreatic duodenectomy (PPPD) and the adequate choice of anastomotic technique are also largely related to the postoperative exocrine function of the pancreatic residue. Pancreatic exocrine insufficiency is a manifestation of many pancreatic diseases and is associated with a deficiency of micronutrients and fat-soluble vitamins. Enzyme replacement therapy was associated with improved survival compared to control groups

of patients in multiple studies [91]. Due to the scarce and contradictory studies on the dynamics of pancreatic exocrine secretion after pancreatoduodenectomy for neoplasms and the lack of an in-depth analysis of their relationship with the type of reconstructive technique, it is expedient from a scientific point of view to investigate them in detail. In this context, it is appropriate to study the relationship of indigestion to tumor growth and metastasis in this type of carcinoma.

2. CONCLUSIONS FROM THE LITERATURE REVIEW

1. Adenocarcinoma of the pancreas ranks fourth as the cause of death from cancer worldwide. In the last decade, there has been a tendency to increase the number of patients with this type of neoplasm. Despite the aggressive multidisciplinary approach to the treatment of PA, the ratio of morbidity to mortality remains unchanged. The survival rate in these patients also remains unchanged.
2. In the available literature, perioperative assessment of pancreatic exocrine capacity is poorly represented.
3. Studies on the exocrine function of the pancreas according to the type of reconstruction have conflicting results, which requires more in-depth research.
4. The consequences of pancreato-gastroanastomosis on the long-term physiology of digestion are insufficiently studied and require further research.
5. Various studies on the relationship of the anastomotic technique used to early postoperative complications have mixed results.
6. The anatomical integrity and functional suitability of the pancreatic canal after duodenopancreatic resection require further clinical studies.
7. The enzyme fecal elastase 1 directly reflects the secretory capacity of the gland with the greatest statistical certainty.
8. Despite the in-depth knowledge of the specific biology of pancreatic adenocarcinoma, the direct effect of pancreatic enzyme deficiency on tumor growth and metastasis has been poorly studied. The above makes it necessary to study the value of maldigestion as an independent prognostic factor in this type of pathology.

3. PURPOSE AND OBJECTIVES

PURPOSE

To investigate exocrine function after pancreatoduodenal resection for neoplasms, postoperative survival, quality of life, the relationship between maldigestion, tumor growth and metastasis, as well as the correlation between the types of reconstructive techniques (pancreatogastro- and pancreatojejunoanastomosis) and enzymatic activity.

OBJECTIVES

1. To study the demographic and clinical characteristics of the studied contingent of patients;
2. Identification of the most appropriate methods for assessing exocrine function after pancreatoduodenal resection and the degree of reliability in the use of imaging diagnostics and the intraoperative consistency of the gland as an indicator of exocrine function;
3. To study the frequency of exocrine dysfunction after pancreatico-gastroanastomosis and pancreatico-jejunal anastomosis and the frequency of covering the main pancreatic duct by gastric mucosa when using pancreatico-gastroanastomosis;
4. To study the frequency of postoperative complications in both anastomotic techniques, as well as their effect on pancreatic gland reserve;
5. To study the relationship between enzyme insufficiency with the progression of the tumor process and the influence of exocrine insufficiency after pancreaticoduodenal resection on survival and quality of life

4. MATERIALS AND METHODS

4.1. MATERIALS

A retrospective cohort study was carried out for a period of 6 years (2017–2022) at the Clinic of Surgery of the Varna Hospital at the Military Medical Academy. 121 duodenopancreatic resections for neoplasms were performed, and 92 patients with adenocarcinoma of the head of the pancreas were selected for the purpose of the study. The remaining patients were rejected due to non-compliance with the inclusion and exclusion criteria of the study. The selection is by age, sex, tumor size, histological variant, resection line.

Criteria for the selection of patients for the purposes of the study:

- **Including criteria:**
  - TNM stages (1–2 B);
  - Cooperation on the part of the patient;
  - Availability of preliminary data from X-ray and laboratory tests related to the study;
  - R0 resection.
- **Exclusion criteria:**
  - Unresectable tumors;
  - Metastatic tumors.

4.2. METHODS

In order to perform the tasks, the following methods were used:

Preoperative preparation and data collection for the purposes of the study.

Preoperative preparation of patients is carried out according to the standards of good medical practice.

Performance status assessment: This indicator is examined before and after the surgical intervention, comparing it with the data from the assessment

of the exocrine function of the pancreas and the negative changes in the average body weight. For the purposes of the study, the cohort of patients was divided into two groups according to this indicator, with patients with good performance status determined those with a score from 0 to 2. The group with a score between 3 and 4 was categorized as having poor PS. Additionally, performance status was interpreted as an integral part of the dynamic changes in the physical parameters of quality of life among patients with pancreatic adenocarcinoma.

Assessment of hematologic, hemostasiological and biochemical parameters.

Preoperative examination of fecal elastase-1 and determination of the degree of exocrine insufficiency. It is generally accepted. According to this indicator, digestive function should be divided into three categories. Patients with FE-1 levels above 200 micrograms per gram have normal exocrine function. At fecal elastase levels in the range between 100 and 200 micrograms, moderate exocrine insufficiency is present. Exocrine insufficiency is severe in patients with an indicator value of less than one hundred micrograms.

Implementation of a pancreatic scan protocol (NCCN 2019) in order to determine the venous and arterial anatomical criteria for resectability, as well as the absence of metastatic disease.

Discussion of patients by a multidisciplinary team in order to determine the operability and treatment strategy of advanced cases.

Preoperative and intraoperative assessment of pancreatic exocrine function by laboratory analysis and imaging. For the assessment of exocrine pancreatic function, fecal elastase 1 with a sensitivity of 95–100% and a specificity of the method of 65–95% was used preoperatively. With a width of the main pancreatic canal of more than 0.3 cm, measured on CT or ultrasound, preoperatively 92% impaired exocrine function is expected. Intraoperative assessment of pancreatic consistency and pancreatic canal width, determining the degree of correlation of these parameters with exocrine function (Figure 1).

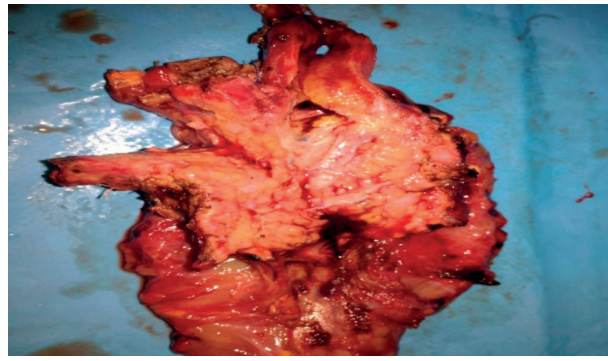


Figure 1. Macroscopic preparation with adenocarcinoma of the head of the pancreas, showing cystically dilated pancreatic duct with a diameter of more than 3 mm and signs of glandular fibrosis

Endoscopic examination of the anatomical integrity and functional fitness of pancreatogastroanastomosis. In cases with pancreatogastroanastomosis, endoscopic diagnostics were performed a month after the intervention in order to determine the frequency of anastomosis covering with gastric mucosa.

Laboratory analysis of postoperative exocrine function and its relation to tumor spread and local recurrence. For the purposes of the study, X-ray screening was used to monitor the frequency of metastasis in patients with exocrine insufficiency, correlated with the studied patients with normal pancreatic function.

Surgical aspects of pancreatic drainage according to the type of reconstruction

Pancreatojejunoanastomosis was performed according to the approved 2014 single-storey duct-to-mucosa anastomosis:

- The pancreatic canal is released from the surrounding parenchyma at a length of 2–3 mm caudally;
- Figure 2 shows the imposition of three sutures through the entire thickness of the parenchyma from the posterior surface of the pancreas and the posterior wall of the pancreatic canal;

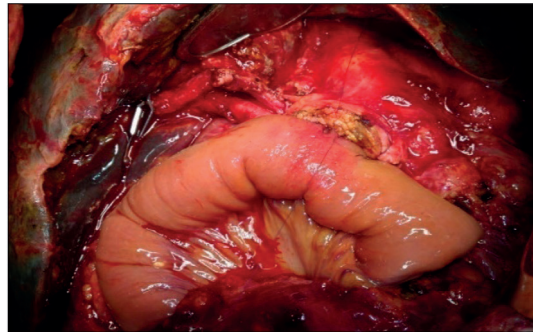


Figure 2. First floor of the posterior wall of the anastomosis

- Figure 3 shows two single sutures that are applied throughout the entire thickness of the pancreatic parenchyma from the anterior wall of the pancreatic canal to the anterior surface of the pancreas. The sutures are 2–3 mm away from the resection line of the pancreatic duct;

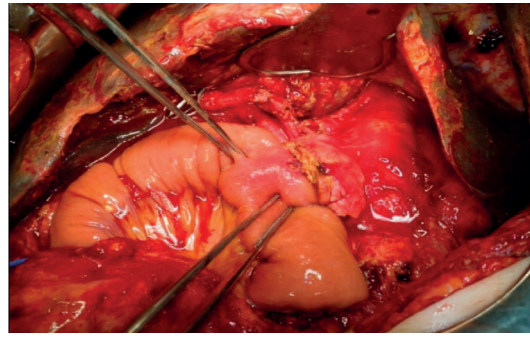


Figure 3. First floor of the anterior wall of the anastomosis

- The posterior wall is sheathed with a series of 4 “mattress” sutures (PDS 4/0) between the pancreatic residue and the seromuscular layer of the jejunum;
- Similar to the posterior wall of the anastomosis, Figure 4 shows the securing of the anterior wall by applying single sutures (PDS 4/0) between the seromuscular layer and the pancreatic tissue.

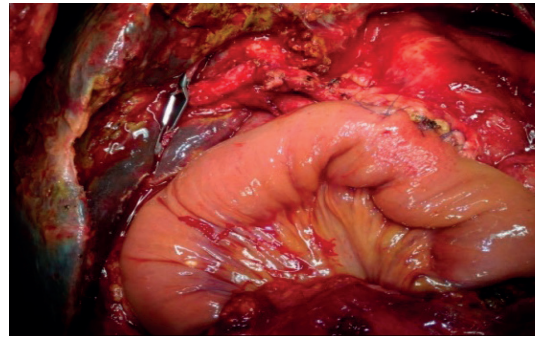


Figure 4. Mattress seams on the front wall of the anastomosis

Surgical technique of pancreatogastroanastomosis

The seamless PGA was first introduced in 2015. and is carried out in five steps:

- Figure 5 shows the pancreatic residue released from the surrounding tissues and the lienal vein, all visible vessels in the resection area are sutured.

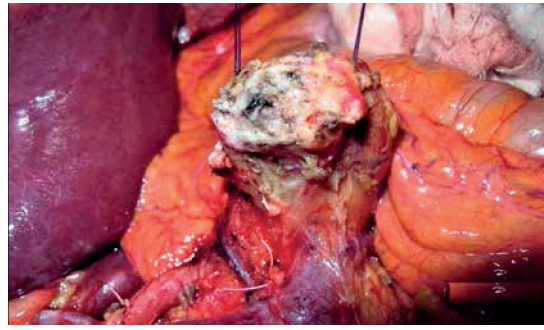


Figure 5. Pancreatic residue prepared for implantation in the gastric cavit

- Figure 6 shows the stomach open along the posterior wall as part of preparation for the anastomosis;

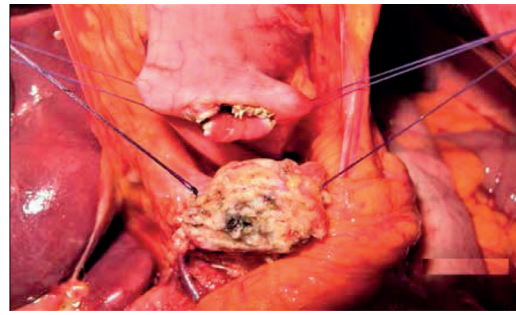


Figure 6. Posterior gastrotomy

- Figure 7 shows the imposed bag suture with monofilament thread, which will ensure the tightness of the anastomosis;
- Figure 8 shows the withdrawal of pancreatic residue into the gastric cavity using an incision along the anterior gastric wall;

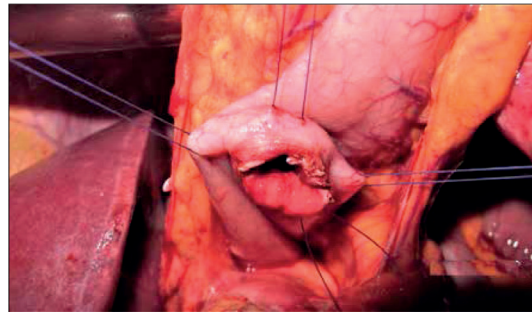


Figure 7. Applying a gastrotomy bag suture

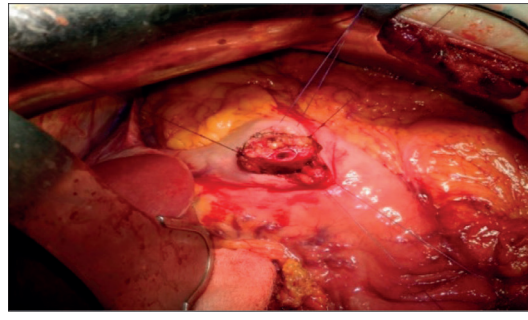


Figure 8. Pancreatic residue brought into the gastric cavity

- Figure 9 shows the completed seamless anastomosis, the sealing of which is achieved by elastic tightening of the bag seam.

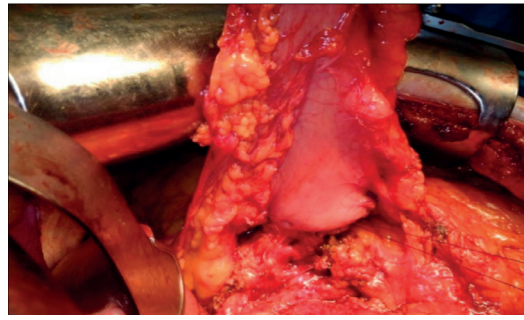


Figure 9. Elastic tightening of the bag seam

If there is no tumor infiltration that hinders the surgical approach, pyloric storage duodenopancreatic resection was performed in the studied group of patients. Pyloric storage should lead to improved pancreatic exocrine function in both types of anastomotic technique used. Intraoperative ultrasound was used in the studied patients with a view to further assessing the resectability of the tumor formation and re-rejection of metastatic disease [1]. In this way, a similar TNM stage is once again ensured in the studied group of patients.

In both types of anastomotic techniques, three contact drains are placed. The drainage of the pancreatic anastomosis is taken to the left. The remaining two drains are positioned above and below the hepatoduodenal ligament and are taken to the right.

Pancreatogastroanastomosis drains independently by isolating it in a separate compartment from the mesenteric-portal vessels.

Postoperative complications in the study are defined according to the ISGPS and Dindo-Clavien classifications. For the purposes of the study, cases of fistula type B and C, intraluminal and extraluminal hemorrhage types B and C, intra-abdominal abscess, acute postoperative pancreatitis and impaired gastric emptying were examined. The frequency of these complications in both types of anastomotic techniques has been studied.

Special attention is paid to complications associated with pancreatic anastomosis insufficiency and postoperative acute pancreatitis, as they are expected to lead to atrophy of the pancreatic residue.

On the first postoperative day, amylase activity from the declinal of the pancreatic anastomosis drain is examined.

Tracking hospital stays and days of intensive observation and treatment. Comparison of these indicators with the complications that occurred as a result of pancreatic anastomosis insufficiency.

Dynamic study of significant weight loss during the first postoperative year. A comparison of this indicator with the dynamics of loss of pancreatic exocrine function is imperative to be carried out in order to assess the relationship between these indicators, as well as their attitude to the performance status of patients and the quality of life after surgery.

Monitoring of postoperative dynamics in the performance status of patients, correlated with digestive disorders in the one-year follow-up period.

Survival and mortality rates were examined within a year for the purposes of the study. This is necessary due to the comparison of these parameters with the complications of surgical intervention, the development of the oncological process and exocrine function. Characteristic of pancreatic adenocarcinoma are low average survival and high mortality. Guided by this fact, despite the deviation from the generally accepted follow-up frameworks, an optimal cohort of patients is obtained, which would lead to statistical reliability of the analysis.

The statistical methods used for the purposes of the study are:

1. **Descriptive statistics** – mean, standard deviations, row widths and degree of balance of the sample.
2. **Percentage Ratios and Distributions.**
3. **Correlation analysis.**
4. **T-test for comparison of the studied groups.**
5. **Kaplan-Meyer survival test.**

All statistical analyses were made on a confidential basis 95% interval

5. RESULTS

For the period January 2017 – December 2022, 121 duodenopancreatic resections for neoplasms were performed in the Clinic of Surgery of the Hospital – Varna at the Military Medical Academy, and for the purpose of the study, 92 patients with adenocarcinoma of the head of the pancreas were selected.

5.1. GENERAL CHARACTERISTICS OF THE SAMPLE (DESCRIPTIVE STATISTICS)

5.1.1. Middle age – the distribution of patients included in the study by age is similar to the results in the literature. The minimum age of those affected is 41 years and the maximum is 83 years (Figure 10)

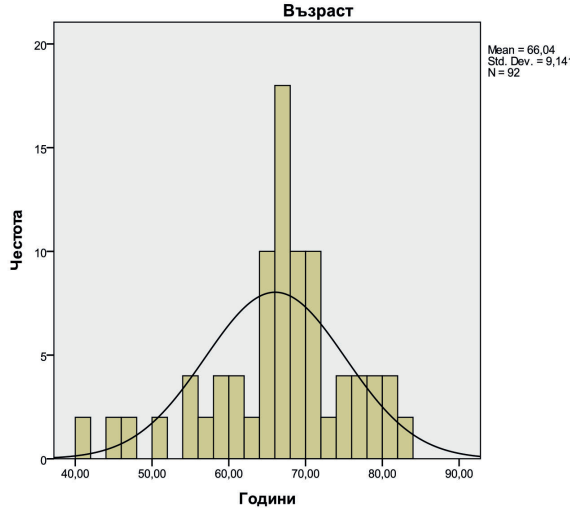


Figure 10. Histogram of the distribution of the sample by age

Table 1. Distribution of patients by age

брой	**92**
средно	66,0435
стандартно отклонение от средната	9,14104
минимум години	41,00
максимум години	83,00

The data from figure 10 and table 1 indicate that the sample is relatively close to a normal distribution based on the age criterion. The variance (deviation from the mathematical expectation) is relatively small in relation to the mean value, which suggests freedom in the use of parametric and non-parametric statistical methods.

Gender - the relative proportion of men affected by pancreatic adenocarcinoma is insignificantly lower than that of women in the studied cohort of patients. The sample is relatively balanced by gender. In further statistical comparisons between the two groups, the number of women will be randomized to n = 42 at random (table 2).

Table 2. Percentage ratios by gender

	Честота	**Процент**
Мъже	42	45,7
Жени	50	54,3

Figure 11 shows the percentage distribution by sex for the two anastomotic techniques used in the study.

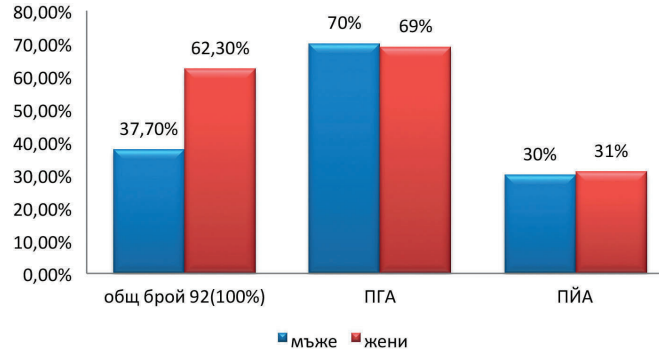


Figure 11. Percentage distributions by sex by type of the anastomosis performed

Data from the statistical analysis in Figure 11 show that patients with pancreatogastroanastomosis are more than those with pancreatojejunoanastomosis. This is due to the individual technical preferences of the individual surgeons who performed the interventions in the examined contingent of patients. Regardless of this fact, the groups were selected to be equivalent in terms of sex.

5.2. CLINICAL PICTURE OF PATIENTS WITH PANCREATIC ADENOCARCINOMA INCLUDED IN THE STUDY

Worldwide, mechanical icter is the most common symptom requiring a deeper clinical search aimed at making a diagnosis of pancreatic adenocarcinoma. The latter is indicative of the long quiet course of development in this type of neoplasm. High levels of CA 19–9 could be indicative of diagnosis in the preclinical stages of PA, but have been rejected as screening for this disease in the available literature due to their characteristic sensitivity and specificity.

5.2.1. Mechanical icter

Mechanical icter is the first manifestation of the disease in 82.60% of the studied cases that developed this symptom

Table 3. Percentage of icteric patients in the study

	Честота	Процент
Иктерични	64	74,4
Аниктерични	22	25,6

In the course of a study of the common symptoms leading to the diagnosis of pancreatic head cancer, it was found that in 74.4% (n = 64) of cases, the diagnosis was made as a result of clarification of patients with mechanical jaundice (Table 3). This brings out hyperbilirubinemia of increasing intensity as one of the most common symptoms in the study. This clinical manifestation necessitated the use of a diagnostic algorithm for the pancreas in this sample of patients.

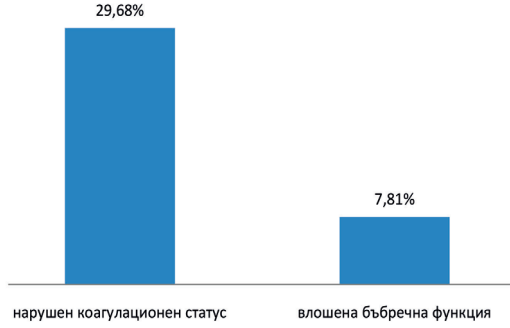


Figure 12. Percentage distribution of complications associated with mechanical icter

In 29.68% of icteric patients, impaired coagulation status was found, a result of impaired liver synthetase function. In 7.81% of these patients, we recorded impaired renal function with elevated urea and creatinine values, abnormalities in blood gas analysis and ionogram (Figure 12).

Preope c rative bile tree encumbrance in the studied contingent is present in 30% of cases (Figure 13). As a reason for these actions, intensive icter and subsequent severe blood clotting disorders in these patients are highlighted. Part of this group are categorized as unresectable in other hospitals and underwent palliative surgery.

Figure 13. Percentage of patients undergoing preoperative bile drainage to the total number of patientswith mechanical icter

Figure 14 shows the percentage of patients with clinical and microbiological data for cholangitis after biliary decompression prior to radical surgery. Statistical analysis shows that only 30% of the studied group are free of cholangitis. The most commonly isolated causative agents from the bile ducts in patients with cholangitis, the subject of the study, are gram-negative microorganisms from the Enterobacteriaceae group.

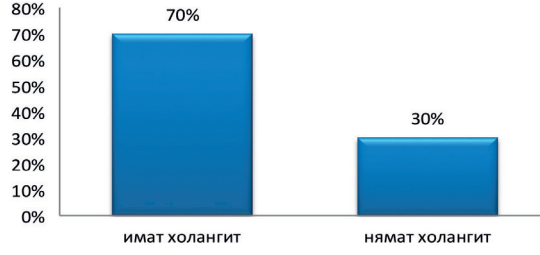


Figure 14. Percentage of patients with cholangitis compared to the control group of icteric patients

Cholangitis emerged as one of the independent risk factors for postoperative complications after Whipple's surgery in the studied contingent of patients. Timely etiological diagnosis and radical surgical intervention in icteric patients would reduce the risk of these complications.

5.2.2. Chronic pancreatitis – often the clinical manifestation of pancreatic carcinoma is masked by underlying chronic pancreatitis. The following results are in confirmation of the latter:

Table 4. Percentage ratio of patients diagnosed with chronic pancreatitis compared to all patients with this pathology in the study

	Честота	Процент
Диагностицирани	10	19,2
Новооткрити	42	80,8

From the analysis performed (Table 4) of the subgroup of patients with histologically confirmed chronic pancreatitis postoperatively, it was found that only 19.2% of the examined have been diagnosed or have developed a symptom complex indicating such. Most likely, this is due to the absence of characteristic complaints in patients with moderate exocrine insufficiency associated with digestive disorders and the absence of pain syndrome in this sample of patients.

In a large part of patients with chronic inflammatory process of the pancreas, concomitant exocrine disorders are found. Exocrine insufficiency, chronic inflammation and often concomitant diabetes are accepted as a prerequisite for poor pancreatic reserve preoperatively.

The statistical analysis of the studied patients showed the following trends:

Table 5. Percentage ratio of patients with chronic pancreatitis compared to the control group of patients in the study

	Честота	Процент
Хроничен панкреатит	52	60,5
Контролна група	34	39,5

In the course of the study, 60.5% of the subjects had underlying chronic pancreatitis, detected histologically after surgery (Table 5.). This result confirms the association identified in the review of the literature on chronic pancreatitis with the initiation of neo-oncogenesis in PA. However, the impaired patency of the main pancreatic duct in some patients should be taken into account, which leads to atrophy and fibrosis of the organ. In 39.5% of the examined, cancer occurs against the background of an intact pancreas. These data give reason to study more deeply the etiopathogenesis of the occurrence of pancreatic adenocarcinoma against the background of normal glandular parenchyma.

5.2.3. Impaired exocrine function

The contingent of patients included in the study is divided into three groups according to the degree of exocrine insufficiency preoperatively, in order to track in which of them the VDR receptor mechanism (lack of fat-soluble vitamin D) is a possible cause of the tumor process.

Table 6. Preoperative percentage of patients with pancreatic adenocarcinoma by exocrine function criterion

	Честота	Процент
FE-1 < 200	**64**	**69,6**
FE-1 > 200 µg/g	28	30,4

From the statistical analysis (Table 6) of patients preoperatively according

to the criterion of exocrine function, it was found that in 69.6% of cases there was exocrine insufficiency. Normal exocrine function was demonstrated by 30.4% of the examined. From these results, it can be concluded that in 69.6% of the analyzed there is a deficiency of vit. D, which makes possible the VDR receptor mechanism for initiation of the neoplastic process in this part of the subjects.

5.2.4. Weight reduction

Weight reduction was reported as the second most common symptom in the study with important prognostic significance. The latter was found in 73.91% (n = 68) of cases, and was combined with exocrine pancreatic insufficiency in 82.4% (n = 56) of patients.

Figure 15. preoperative weight loss is shown in the two anastomotic techniques used. These data are significant due to their correlation with secretory disorders of the pancreas..

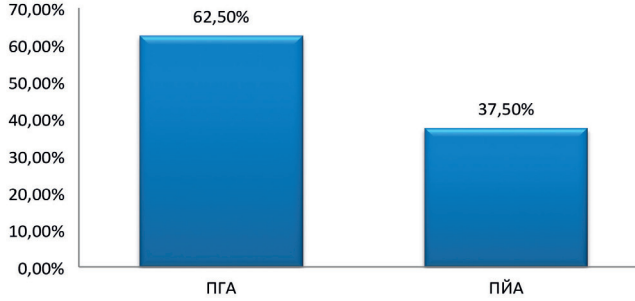


Figure 15. Preoperative significant weight loss

Table 7. Ratio of body mass loss in PA patients to exocrine function

	Честота	Процент
FE-1 < 100	56	82,4
FE-1 > 100 µg/g	12	17,6

The following trends are reported in the weight loss factor. Statistical analysis (Table 7) shows that 82.4% of patients with a loss of more than 10% of their body weight for 6 months have severe exocrine insufficiency, and 17.6% have FE-1 levels above 100 μg/g.

5.2.5. Digestive disorders – An anamnestically established symptom complex indicating digestive disorders was observed in 80.8% of the examined, which indicates a direct correlation with the measured levels of fecal elastase in these patients. Abdominal discomfort, colicky pain and flatulence as an expression of maldigestion were found in 48.07% of patients with impaired exocrine function, and these complaints lead to accidental diagnosis of the neoplasm in 3.26% of this group of patients.

5.2.6. Impaired endocrine function

Table 8. Percentage ratio of diabetics to the control group of patients

	Честота	Процент
Захарен диабет	46	53,5
Нормогликемия	40	46,5

The statistical analysis showed that in 53.5% of the studied cases, diabetes mellitus was present preoperatively. In 46.5% of patients, normal blood sugar values were observed during biochemical analysis (Table 8).

Table 9. Prevalence of diabetes in the studied patients with chronic pancreatitis

	Честота	Процент
Захарен диабет	24	46,2
Контролна група	28	53,8

An additional study of the incidence of insulin-dependent diabetes mellitus in the studied contingent of patients with chronic pancreatitis preoperatively showed that 46.2% of patients with chronic pancreatitis also have high blood sugar values. 53.8% of the study group did not have concomitant diabetes (Table 9). These data are important for differentiating the contingent with combined pancreatic insufficiency. The latter indicates a poor reserve of the pancreas and is an unfavorable prognostic sign in these patients.

5.2.7. Preoperative disorders in performance status

For the purposes of the study, performance status (PS) is divided into good (score 1–2) and bad (score 3–4)..

Table 10. Distribution of patients with PS = 3 and 4 according to exocrine function factor

	Честота	Процент
FE-1 < 100	60	83,3
FE-1 > 100 μg/g	12	16,7

In 83.3% of the examined patients with performance status 3 and 4, severe exocrine insufficiency was preoperatively detected (Table 10), which indicates a connection of impaired digestion in these patients to their general condition with moderate and severe degrees.

5.3. PREOPERATIVE IMAGING

5.3.1. X-ray criteria for chronic pancreatitis and exocrine pancreatic disorders

For the purposes of the study, the ratio of the diameter of the common pancreatic canal to the categorized cases with a “hard” pancreas during the surgical intervention was investigated. The purpose of this statistical

analysis is to establish whether a diameter of more than 3 mm, reported by scan graphs, corresponds to patients with chronic pancreatitis and exocrine insufficiency.

Table 11. Exocrine function in patients with a pancreatic duct diameter greater than 3 mm

	Честота	**Процент**
FE-1 < 200	60	96,8
FE-1 > 200 μg/g	2	3,2

With a size of the main pancreatic canal of more than 3 mm, the studied cases demonstrate 96.8% exocrine insufficiency clinically and in laboratory tests performed preoperatively (Table 11). These results lead to the conclusion that this parameter can be used with a high degree of confidence to predict pancreatic exocrine function.

Table 12. Ratio of pancreatic consistency to pancreatic duct diameter

	Честота	**Процент**
„твърд“ панкреас	46	74,2
„мек“ панкреас	16	25,8

In 74.2% of the studied cases with a diameter of the main pancreatic duct of more than 3 mm, a “hard” pancreas was observed intraoperatively (Table 12). This result gives grounds for the parameter to be used with great credibility in the preoperative planning of an appropriate method for pancreatic reconstruction after duodenopancreatic resection.

The study analyzes the relationship of exocrine function to the subjective intraoperative criterion “hard” pancreatic parenchyma. The purpose of this

comparison is to be able to use pancreatic consistency as an indication of the exocrine capacity of the pancreas.

Table 13. Exocrine function levels in patients with pancreatic atrophy included in the study

	Честота	Процент
FE-1 < 100	46	88,5
FE-1 > 100 μg/g	6	11,5

During the statistical analysis of the results obtained in the studied group of patients, it was found that in 88.5% of the cases, patients with imaging diagnostic criteria corresponding to a hard pancreas preoperatively had fecal elastase levels below 100 μg/g (Table 13). These results rank preoperative scan data for pancreatic atrophy and the width of the main pancreatic duct as reliable indicators of pancreatic exocrine function and underlying chronic pancreatitis. These conclusions need to be considered critically due to the nature of the study.

For the purposes of the study, a comparative analysis was carried out to determine the degree of overlap of the scan criteria for chronic pancreatitis with the definition of "hard" pancreas.

Table 14. Scan criteria for chronic pancreatitis

	Честота	Процент
Панкреасна атрофия	52	56,5
Без данни за атрофия	40	43,5

Table 15. Intraoperative finding

	Честота	Процент
„твърд“ панкреас	48	52,2
„мек“ панкреас	44	47,8

Correlation (Spearman's rho)

	Предоперативни критерии за твърд панкреас	Вид на панкреаса интраоперативно
CT критерии за твърд панкреас	1,000	,916** Sig. (2-tailed),000
Текстура на панкреаса интраоперативно	,916** Sig. (2-tailed),000	1,000

**. Correlation is significant at the 0.01 level (2-tailed).

The comparative analysis presented in Tables 14 and 15 shows that there is a very strong correlation between the imaging diagnostic criteria for chronic pancreatitis and the intraoperative definition of the pancreas as “hard” in the study ($r = 0.916$; $p < 0.001$). These results indicate compliance with the CT criteria for a rigid pancreas (uneven dilation and diameter of more than 3 mm of the main pancreatic canal, as well as evidence of pancreatic atrophy and calcifications) with its intraoperative consistency. The analysis carried out gives grounds to use these data for orientation in the choice of anastomotic technique preoperatively.

In patients with significant weight consumption, scan scans of pancreatic atrophy and an increased pancreatic duct diameter of more than 3 mm were found among the subjects (Figure 17).

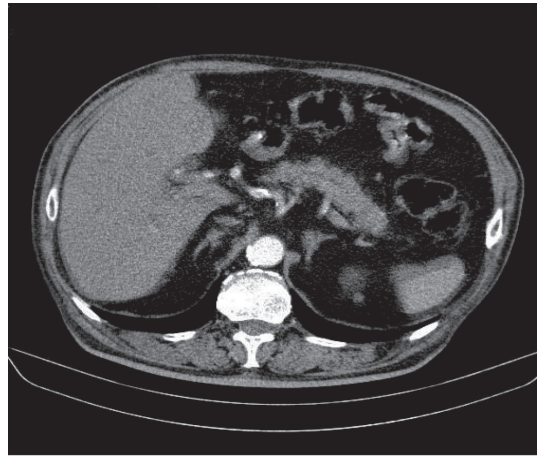


Figure 16. Patient with pancreatic adenocarcinoma without scan criteria for underlying chronic pancreatitis

Figure 17. Scan image of chronic pancreatitis. Pancreatic atrophy and unevenly cystically dilated main pancreatic canal in a patient with PA

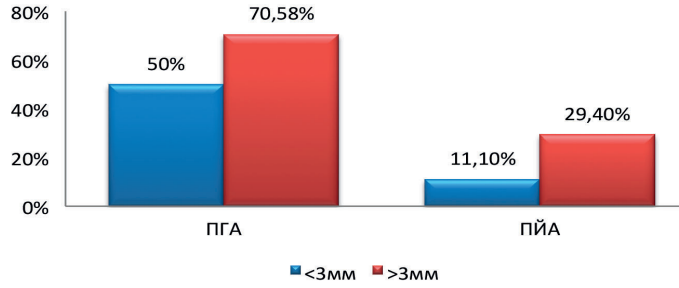


Figure 18. Pancreatic duct diameter

Figure 18 shows the distribution of the measured diameter of the pancreatic duct preoperatively in the two types of pancreatic residue anastomosis techniques compared in the study.

In summarizing the results obtained from the above analyses, the following conclusion can be drawn: the degree of pancreatic atrophy and the diameter of the pancreatic duct, established by scaneography, are criteria that speak with a high degree of credibility for an underlying exocrine insufficiency based on chronic pancreatitis.

The statistical results give reason to consider the wider use of scanner criteria for chronic pancreatitis in the context of establishing exocrine insufficiency in patients with pancreatic adenocarcinoma.

5.3.2. Imaging and diagnostic analysis aimed at confirming the diagnosis of PA in the examined sample of patients

When establishing a clinical picture indicating pancreatic adenocarcinoma among the patients studied, a pancreatic scan protocol (NCCN) was performed. In case of suspicion of a generalized process or inoperability, the diagnosis is supplemented with MRI. In n = 8 patients, metastatic disease was found and excluded from the study. Twelve (n = 12) of the patients with arterial and/or venous anatomical criteria for infertility also dropped

out of the study. After determining the degree of neoplasm spread, the patients were discussed by a multidisciplinary team in order to specify the therapeutic behavior.

5.4. TYPES OF SURGICAL INTERVENTIONS

After determining the operability of the patients, all participants in the study underwent duodenopancreatic resection with standard lymphatic dissection. For the entire contingent, a margin of tumor cell-free tissues was achieved, at a distance of 1 cm from the line of resection (cauterization), which guarantees R0 resection in all patients. In 3.26% (n = 3) of the cases, partial or complete resection of an extrapancreatic organ was required due to oncological expediency. 2.17% (n = 2) of the subjects underwent portal vein resection followed by vascular reconstruction. Pyloric preservation procedure was not performed in 10.86% (n = 10) of cases due to oncological inexpediency. In all patients with preoperative bile derivation, material was taken for microbiological analysis during the surgical intervention.

5.5 PERIOPERATIVE DETAILS RELATED TO THE RECONSTRUCTIVE TECHNIQUE

5.5.1. Pancreatogastroanastomosis was performed in 63% of patients. The average operative time of the intervention was 4.1 hours. Intraoperative blood loss in the group was as follows: < 500 ml – 84.29%; 500–1000 ml – 13.22%; > 1000 ml – 2.47%.

The observed postoperative complications in this type of anastomotic technique are:

- Type C fistula was not detected in this type of anastomosis during the study. Type B fistula was recorded in 14% of those reconstructed by PGA (Figure 19).
- Intraluminal bleeding type C was found in 4% of those examined (Figure 20). In these cases, the cause of hemorrhage is the pancreatic

residue. In them, it was necessary to undertake an anterior gastrotomy with suturing the bleeding vessels of the pancreatic residuum buried in the gastric cavity. Chemotransfusion of more than one sac of erythrocyte concentrate was performed. Extraluminal bleeding and hemorrhage type B in those examined with pancreatogastroanastomosis was not recorded in cases object of the study.

- Impaired gastric emptying was diagnosed in 32% of those operated on (Figure 22).
- An intra-abdominal abscess was recorded in 18% of cases (Figure 21), which required drainage under ultrasound control in 11% of patients. Resurgery was undertaken in 7% of the studied subgroup.

5.5.2. Pancreatojeunoanastomosis was used in 37% of cases. In all patients in this subgroup, anastomosis has been protected by drainage of the main pancreatic channel "Per Due". The average duration of the operative procedure for this operative technique is 4.4 hours. The average blood loss during the intervention is: <500 ml – 81.52%; 500–1000 ml – 15.21%; > 1000 ml – 3.26%.

Complications in PJA in the study contingent of patients:

- type B fistula is registered in 7% of patients. In 7% of the cases studied with this type of anastomosis, the type C fistula (Figure 19) is diagnosed;
- Late extraluminous hemorrhage type C was established in 14% of studied (Figure 20);
- An abdominal abscess is registered in 7% of the reconstructed PJA (Figure 21).

An emergency relaparotomy was undertaken in complications requiring surgery. Totalization was required in 1.08% (n = 1) of cases; The drainage of the abscess cavity under ultrasound control in two of the surveyed - 2.17% (n = 2).

In none of the patients, it resorted to the pancreatic removal. Extralluminal bleeding in patients involved in the study is not the result of the development of epigastric vascular highways and is controlled through standard ways of hemostasis. More than 3 erythrocyte mass has been used to correct hematological abnormalities.

In the statistical comparison of the two anastomotic techniques, the following trend was identified:

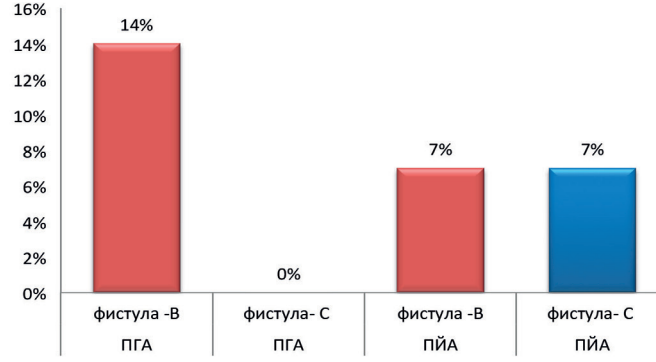


Figure 19. Distribution of patients with POPF in both types of reconstruction

Statistics in the study (Figure 19) indicate twice as high as fistula type B Type B in patients undergoing pancreatogastomosis (14%) compared to the PJA group (7%). None of the studied patients with the reconstruction of the PGA has developed a complication classified as a type C fistula. Compared to the above data, in 7% of cases of pancreatojeunoanastomosis, a reoperation was required for the type C fistula.

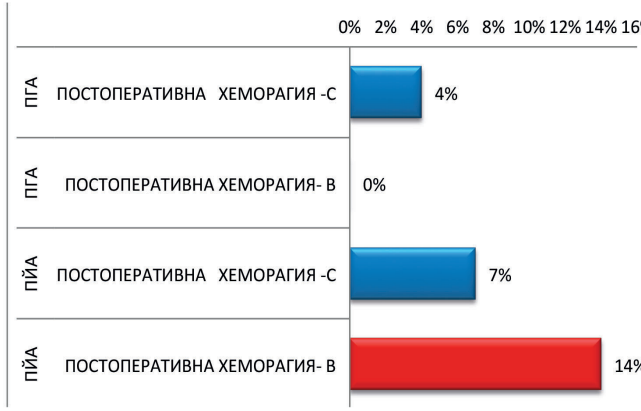


Figure 20. Distribution of the frequency of postoperative hemorrhage (ISGPH) in both types of reconstruction techniques

Statistics (Figure 20) indicate that postoperative hemorrhage type C develops in 4% of cases of PGA among the examination of patients. The fact that in all, it manifests itself with intraluminal bleeding with a source of pancreatic hammer, makes it necessary to process it and thoroughly sewn all vessels in the area. Comparison with pancreatogastomosis, in pancreatojeunoanastomosis, a statistically significant growth in the frequency of this complication is registered - 7%, all categorized as extraluminal bleeding.

In the studied patients with the PGA, no postoperative hemorrhage type B has been detected. Comparison is the latter complication in 14% of cases with PJA (Figure 20).

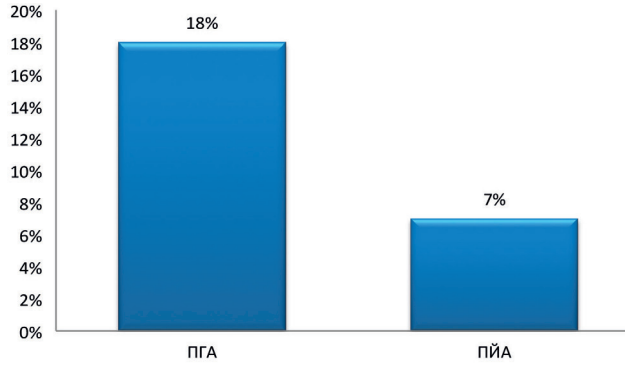


Figure 21. A percentage ratio of intraabdominal abscesses according to the anastomotic technique used in the contingent studied

Statistical analysis shows a higher incidence of intraabdominal abscess in the group subjected to pancreatogastroanastomosis (18%), compared to the one with PJA reconstruction (7%) (Figure 21).

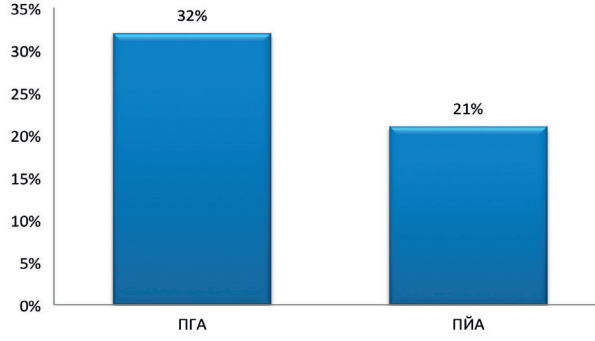


Figure 22. A percentage ratio of impaired gastric emptying in the two types of anastomoses used in the study

Statistical results indicate a higher incidence of impaired gastric emptying in anastomozed by pancreatogastomosis (32%) compared to those with PJA (21%) (Figure 22). This is probably a consequence of details related to

the anastomotic technique itself and the degree of denervation of thecompartment during the destructive phase of the intervention. It is imperative that pyloric dilation be performed at PPPD and two anastomoses used in order to avoid this complication.

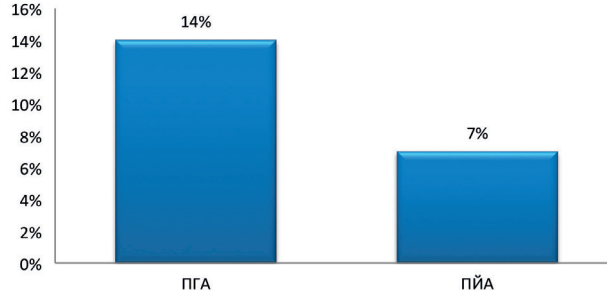


Figure 23. Distribution of postoperative acute pancreatitis among the two groups of anastomotic techniques

Statistical analysis (Figure 23) demonstrates that in the postoperative period, acute pancreatitis developed 14% of the reconstructed pancreatogastomosis and only 7% of those with pancreatojeunoanastomosis. The twice the higher frequency of postoperative pancreatitis in the PGA group is probably due to the devascularization of the pancreatic residue-to a 3 sm of the resection line, which further damages the blood supply to the pancreas. Disturbed networks of collateral circulation due to surgery should also be taken into account. The clinic in this type of complication is similarly similar to that of postoperative pancreatic fistula, leads to scanning verified atrophy of the pancreatic residue and impairs exocrine function in the patients examined.

For the purposes of the study of complications, which supposedly lead to the deterioration of pancreatic exocrine function, the incidence of pancreatic atrophy in the type B and C fistula is analyzed.

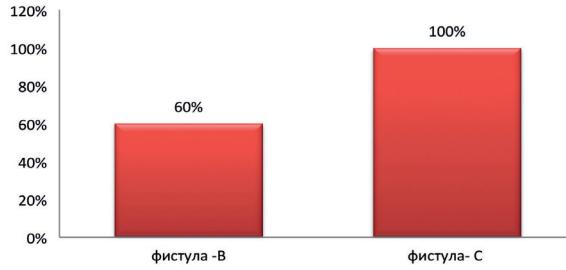


Figure 24. Postoperative pancreatic atrophy in clinically significant pancreatic fistulas

In the study of patients who have developed complications related to pancreatic anastomosis insufficiency, it was found that 60% of patients with type B fistula develop scanned pancreatic atrophy. Pancreatic atrophy due to type C fistula is registered with all studied (Figure 24). These groups of patients demonstrate impaired exocrine function in the postoperative period.

Statistical data processing (Table 16) shows a higher share of severe complications in Class IIIb and IV in Dindo-Klavien in patients undergoing pancreaticojeunoanastomosis, which summarizes the above results.

Table 16. Distribution of complications in the two types of reconstructive techniques according to the classification of Dindo-Clavian

	ПГА	**ПЙА**
Степен II	46%	42%
Степен IIIa	18%	7%
Степен IIIb	4%	14%
Степен IV	0%	2%

In the course of the study, the hospital stay was analyzed in patients with postoperative complications with a view to their impact on the quality of life in the sample studied.

Table 17. General and postoperative average hospital stay in patients with postoperative fistula type B

Фистула тип „B”	**Общ**	**Следоперативен**
Средна стойност	20,6667	13,6667
Стандартно отклонение	5,50757	3,05505

Table 18. General and postoperative average hospital stay with a control group of patients

Контролна група	**Общ**	**Следоперативен**
Средна стойност	15,1500	11,7500
Стандартно отклонение	4,57165	4,07462

Statistics indicate an extension of the total hospital stay in patients who have developed postoperative type B type, an average of 5.5167 days. The postoperative average hospital stay in these patients is extended by 1.9167 bedrooms relative to the control group (Table 17 and 18).

Table 19. General and postoperative average hospital stay in patients with postoperative fistula type C

Фистула тип „C”	**Общ**	**Следоперативен**
Средна стойност	21,7500	19,2500
Стандартно отклонение	5,90903	6,55108

Table 20. General and postoperative average hospital stay with a control group of patients

Контролна група	Общ	Следоперативен
Средна стойност	14,8974	11,1282
Стандартно отклонение	4,24757	2,84863

Statistical analysis in cases of postoperative type C fistula indicates an extension of the total hospital stay by 6,8526 days over the patient‘s control group. The postoperative hospital stay in these patients was extended by 8,1218 days (Table 19 and 20).

Table 21. General and postoperative average hospital stay in patients with postoperative hemorrhage type B

Хеморагия тип „В”	Общ	Следоперативен
Средна стойност	15,5000	12,0000
Стандартно отклонение	7,77817	1,41421

Table 22. General and postoperative average hospital stay with a control group of patients

Контролна група	Общ	Следоперативен
Средна стойност	11,5366	8,9756
Стандартно отклонение	4,74393	4,08343

The statistical analysis of patients with postoperative hemorrhage type B indicates an extension of the total hospital stay by an average of 3.9634 days. The postoperative stay of these patients was increased from the control group by 3.0244 days (Table 21 and 22).

Table 23. General and postoperative average hospital stay in patients with postoperative hemorrhage type C

Хеморагия тип „С”	0бщ	Следоперативен
Средна стойност	23,5000	18,5000
Стандартно отклонение	3,53553	,70711

Table 24. General and postoperative average hospital stay with a control group of patients

Контролна група	0бщ	Следоперативен
Средна стойност	15,1463	11,5610
Стандартно отклонение	4,51421	3,82131

Statistical analysis shows an extension of the total hospital stay in patients with hemorrhage C on average by 8,3537 days over the control group. In these cases, the postoperative stay is extended by 6,939 days (Table 23 and 24). For the purposes of the study, the hospital stay was further analyzed according to the reconstructive technique used:

Table 25. General and postoperative average hospital stay in patients with PGA

ПГА	0бщ	Следоперативен
Средна стойност	15,2857	11,7500
Стандартно отклонение	4,87516	4,35996

Table 26. General and postoperative average hospital stay in patients with PJA

ПЙА	0бщ	Следоперативен
Средна стойност	16,0000	12,1333
Стандартно отклонение	4,73588	3,39888

Statistics show comparable results when taking into account the hospital stay of the two groups of patients. However, there is an extended general hospital stay in the PJA group with 0.7143 days and postoperative hospital stay with 0.3833 days (Table 25 and 26).

Intraoperatively registered "hard" pancreas in 26.60% of patients with pancreatogastomosis and in 73.30% of cases with pancreatjeunoanastomosis.

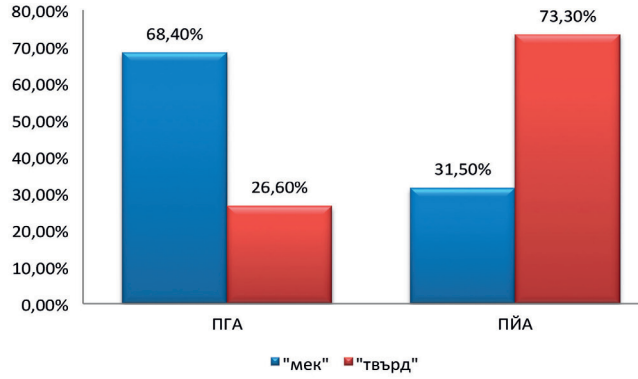


Figure 25. Type Pancreas intraoperatively

Figure 25 presents the distribution of intraoperatively established pancreatic consistency according to the type of reconstruction method used. It is clear that the technique used is largely dependent on the individual preferences of the operator. The latter fact leads to a more accurate statistical analysis of the distribution of complications in the two subgroups. It is known that PGA is a safer method of reconstruction in the case of "soft" pancreatic texture.

In monitoring the dependence of postoperative complications in the conditions of mechanical icter and among anicteric patients in the study, the Statistical Analysis showed the following dependencies:

Table 27. Postoperative complications in icteric and anicheric patients

	Честота	Процент
Аниктерични	6	7,9
Иктерични	70	92,1

The analysis of postoperative complications in the studied group of patients shows a statistically significant difference in the percentage ratio in the group with icter - 92.1%, attributed to the aniceric 7.9% (Table 27). This is most likely due to impaired hepatic synthetic function leading to tissue edema and reduced reparation in the anastomosis area. Another supposed cause could be impaired hemostasiological function in these patients leading to an increased incidence of postoperative hemorrhage.

Table 28. A percentage of patients developed type C fistula having mechanical jaundice

	Честота	Процент
С иктер	76	100,0

For the purpose of the study, the frequency of the “C” fistula in icteric patients was examined. All patients with the above complication were found to have mechanical jaundice in the preoperative period (Table 28). The significance of this complication in the study is related to its attitude to severe pancreatic atrophy postoperatively.

From the analysis performed, the icter can be reliably distinguished as a risk factor for postoperative complications in the studied contingent of patients.

5.5.3. Risk factors for postoperative complications

During the study as a result of the statistical analysis, the mechanical icter is distinguished as an independent risk factor for the occurrence of postoperative complications.

In the qualitative examination and examination of individual clinical cases, the following trends were found:

- In patients with diabetes mellitus, general surgical complications were more observed.
- Patients with a larger T-stadium of the disease show a tendency for more common significant postoperative complications.
- Patients with pronounced consumable syndrome and maldigia, the result of severe pancreatic exocrine failure, show a tendency for both general surgical complications and postoperative complications from the ISGPS section.

5.5.4. Pathologanatomical analysis showed advanced pancreatic fibrosis and loss of acinar tissue in 76.08% (n = 70) of the cases under study, which correlates in 56.5% of cases covering the scanning criteria for chronic pancreatitis. Fecal elastase levels - 1 under 200 μg/g are reported in 69.6% of the cases tested. Patients with exocrine insufficiency have found a pronounced stromal reaction of neoplasm during histological examination. Perineural infiltration was found in 90.21% (n = 83) of cases. Metastatic lymph nodes in more than 3 regions (N1) have not been established in the histological results of the patients studied. The average size of the formation in the studied is between 2 cm and 4 cm, which corresponds to T2.

In 87% of cases, moderately -differentiated adenocarcinoma was detected, and in 13% low -differentiated. Grade G 1 and 4 are not registered in the contingent studied.

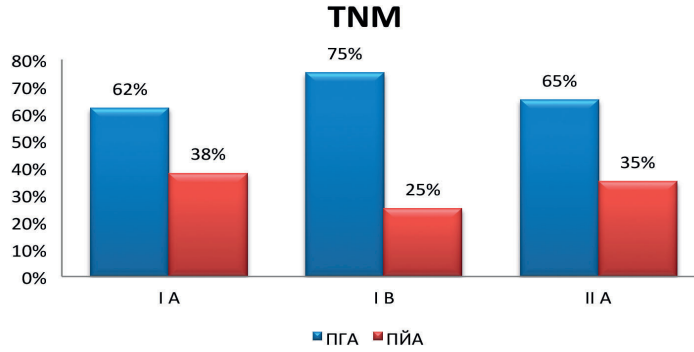


Figure 26. TNM staging for compared anastomotic techniques

In the analysis of the results obtained (Figure 26) came to the following conclusions: In patients stage Ia the relative share of patients with pancreatogatroanastomosis-62% is the higher share of patients with pancreatojeunoanastomosis-38%; In the IB stage, there is the most significant difference in percentage between the two compared excerpts from patients-PGA-75% and PJA-25%; The relative share of patients II A in the reconstructed by pancreatogastroanastomosis is 65% and in 35% of cases pancreatojeunoanastomosis was performed.

5.6. THE DYNAMICS OF EXOCRINE PANCREATIC FUNCTION

For the purposes of the study, the exocrine function of the pancreas was monitored, and Figure 27 shows the general trend in the change of the studied parameter before the intervention and postoperatively in both types of anastomotic techniques. Statistical analysis shows a common tendency for PGA and PIA to deteriorate exocrine function.

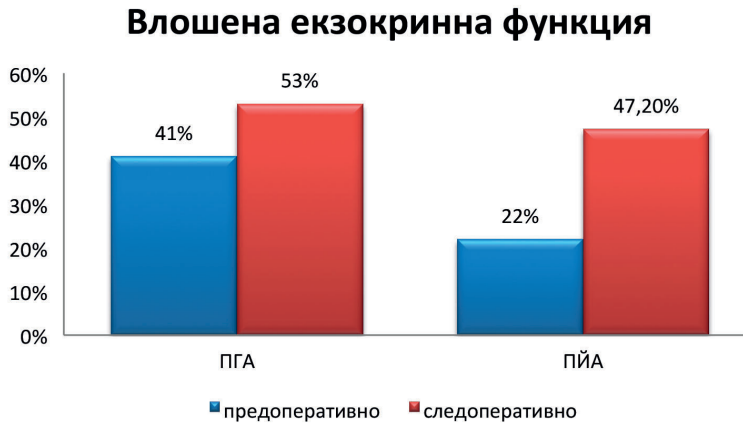


Figure 27. Dynamics of exocrine disorders in the compared anastomoses before and after surgery

Table 29. Preoperative percentage of patients with pancreatic adenocarcinoma according to exocrine insufficiency

	Честота	Процент
FE-1 < 200	64	69,6
FE-1 > 200 µg/g	28	30,4

Table 30. Postoperative percentage of patients with pancreatic adenocarcinoma according to exocrine insufficiency

	Честота	Процент
FE-1 < 200	56	60,9
FE-1 > 200 µg/g	36	39,1

Preoperative exocrine insufficiency was observed in 69.6% of the examined, postoperatively this percentage decreased to 60.9% (Tables 29 and 30). These data confirm the working hypothesis of preserving the exocrine function, comparable preoperatively and in the postoperative period. To

a large extent, this is due to underlying chronic pancreatitis and basally depleted secretory reserve of the gland, therefore, the removal of tumor obstruction of the pancreatic duct does not lead to a complete normalization of the exocrine capacity of the gland.

Table 31. Frequency of PGA coverage by gastric mucosa

	Честота	**Процент**
Мукозна оклузия на панкреатичния канал	20	35,7
Контролна група с панкреатогастроанастомоза	34	64,3

The statistical analysis of the results (Table 31) of fibroscopic follow-up of patients showed that the incidence of mucosal PGA coverage in the study was 35.7% (n = 20). This figure correlates with a deterioration in exocrine function in this sample of patients and FE-1 levels below 100 μg/g. The latter makes sense of a more in-depth analysis of the effect of mucosal resection gastroscopically for the purpose of recanalization of the main pancreatic duct, as well as tracking the consolidation of this effect over time.

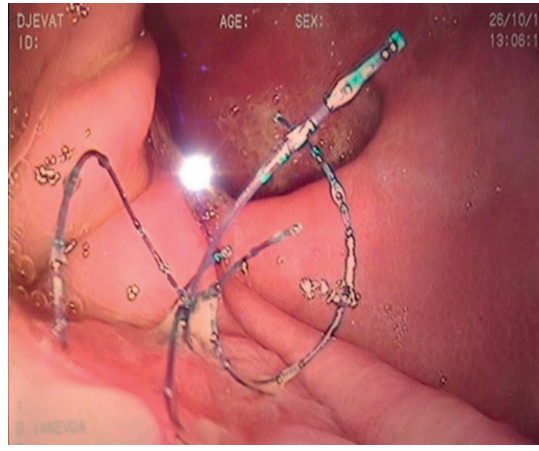


Figure 28. Endoscopy of a patient with gastric mucosa-covered anastomosis

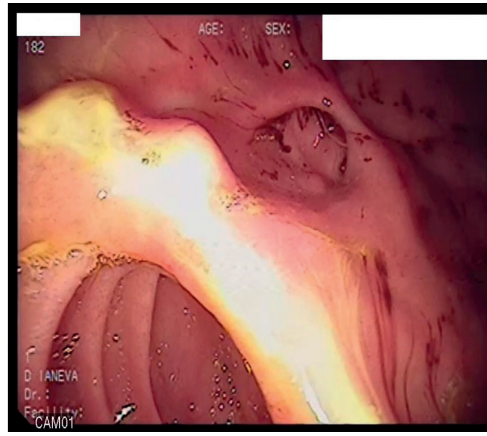


Figure 29. Endoscopy of a patient with pancreatogastroanastomosis, the pancreatic canal is free and secretes pancreatic juice at the time of examination

In patients with compromised pancreatogastroanastomosis due to mucous occlusion of the main pancreatic canal, clinical and laboratory development of severe exocrine insufficiency was established. The exocrine function of the studied patients with PGA reconstruction without covering the anastomosis with gastric mucosa was compared to the group undergoing pancreatojejunoanastomosis. As a result of the analysis, the following conclusions were reached:

- There is a strong correlation ($r = 0.678$; $p = 0.001$) between the recorded decreases in FE-1 below 100 μg/g in the PGA group with the coverage of the pancreatic residue with mucosa in the 1–2nd postoperative month;
- A statistically significant ($t = 2.756$; $p = 0.001$) difference in the postoperative development of severe exocrine insufficiency in the PGA and PJA groups is reported, if excluded patients with mucous blockage of the anastomosis;
- Based on the statistical analysis performed, we can conclude that the deterioration in exocrine function postoperatively in the PGA group is largely due to obstruction of the main pancreatic duct;

- Patients with complications such as postoperative fistula, abscess and pancreatitis were followed up with deterioration of exocrine function with FE-1 levels below 100 μg/g and severe pancreatic atrophy.

In the first postoperative month (Figure 34), against the background of zero mortality in the entire contingent of patients, the following trends were observed:

- Severe exocrine insufficiency (FE-1 levels below 100 μg/g) was recorded in 21.70% of patients undergoing pancreatogastroanastomosis and 15.20% of patients with pancreatojejunoanastomosis;
- Moderate exocrine insufficiency is observed in 17.40% of the PGA-group and in 6.50% of the reconstructed PJAs;
- Normal exocrine secretion is present in 23.90% of patients with pancreatogastroanastomosis and in 15.20% in the group with pancreatojejunoanastomosis.

Deterioration of exocrine function compared to the preoperative period was observed in 12% of those who underwent PGA reconstruction and in 25.2% of those anastomosed by pancreatojejunoanastomosis. This gives grounds to assert that there is a tendency to maintain the levels of preoperative exocrine function in the first postoperative month in those reconstructed by pancreatogastroanastomosis (Figure 26).

In the second postoperative month (Figure 34), a mortality rate of 4.30% was reported in the PGA group and 6.50% of those reconstructed by PJA. There is a decrease in the number of patients with severe exocrine insufficiency (PGA – 17.40% and PJA – 10.90%) due to an increase in the number of patients with moderate exocrine insufficiency (PGA – 17.40% and PJA – 15.20%). A decrease in the number of patients with normal exocrine function in patients with PJA (up to 10.9%) was found and their number was retained in the group undergoing pancreatogastroanastomosis.

In the second month of follow-up, higher mortality and a tendency towards aggravation of disorders in exocrine function were reported in those reconstructed by PJA.

During the third postoperative month, statistics show a doubling of deaths, with an increase of 13% in the PGA group and 15.20% of the studied in the PJA group (Figure 34).

Statistics show that in the PGA group there is a stationary percentage in the three categories of exocrine function. There is a significant decrease of up to 15.20% in patients with severe exocrine insufficiency in the PJA group, while there is a tendency to maintain the number of patients with moderate insufficiency. There was a trend towards a statistically significant decrease in the number of patients with normal exocrine function in the PJA group (14.47%) in the third month (Figure 34).

In the first year, there was a statistically significant difference in mortality in the two patient groups (Figure 30):

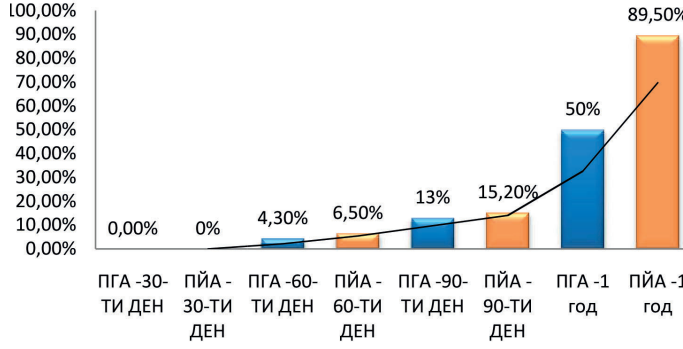


Figure 30. Mortality dynamics during the one-year follow-up period in the two compared groups of patients

Statistical analysis demonstrated the absence of severe exocrine insufficiency in both anastomotic techniques at the end of the first postoperative year (Figure 31):

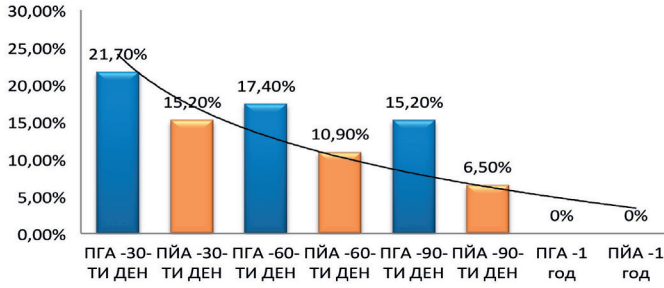


Figure 31. Dynamics of development of severe exocrine insufficiency in the compared groups of patients

Moderate exocrine insufficiency was observed in 2.20% of the PGA group, attributed to 5.30% of those who underwent PJA reconstruction (Figure 32):

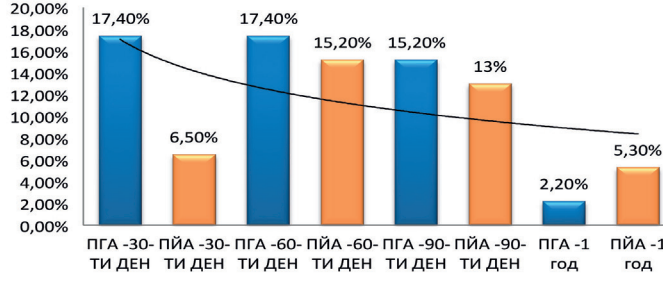


Figure 32. Dynamics of development of moderate exocrine insufficiency in the compared groups of patients

There was no statistically significant difference between the two anastomotic techniques in patients with normal exocrine function (Figure 33):

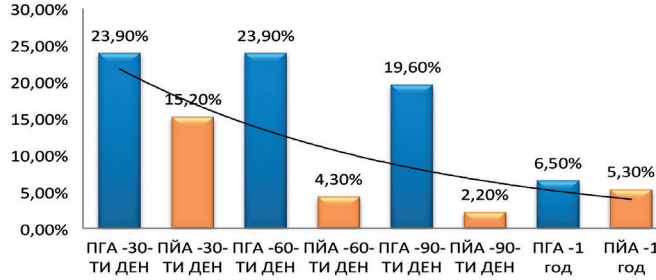
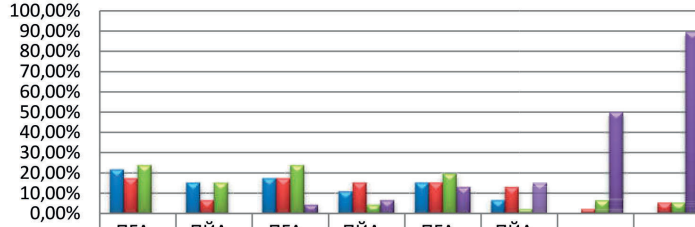


Figure 33. Dynamic follow-up of patients with normal exocrine function in the compared groups

Figure 34 demonstrates the dynamics of exocrine function in both types of anastomotic techniques used in the first year of follow-up. At the same time, mortality during this period of analysis of exocrine capacity was also reported:

Динамика а на екзокринната недостат атъчноъчност



	ПГА - 30-ТИ ДЕН	ПЙА - 30-ТИ ДЕН	ПГА - 60-ТИ ДЕН	ПЙА - 60-ТИ ДЕН	ПГА - 90-ТИ ДЕН	ПЙА - 90-ТИ ДЕН	ПГА -1 год	ПЙА -1 год
ТЕЖКА ЕКЗОКРИННА НЕДОСТАТЪЧНОСТ	21,70%	15,20%	17,40%	10,90%	15,20%	6,50%	0%	0%
УМЕРЕНА ЕКЗОКРИННА НЕДОСАТАТЪЧНОСТ	17,40%	6,50%	17,40%	15,20%	15,20%	13%	2,20%	5,30%
НОРМАЛНА ЕКЗОКРИННА ФУНКЦИЯ	23,90%	15,20%	23,90%	4,30%	19,60%	2,20%	6,50%	5,30%
ПОЧИНАЛ	0,00%	0%	4,30%	6,50%	13%	15,20%	50%	89,50%

Figure 34. Dynamics of exocrine insufficiency and mortality in the compared groups of patients during the one year follow up period

- Substitution therapy was not used in the studied contingent of patients.
- Enzyme substitution does not affect FE-1 levels

Parallel analysis of exocrine function over the one-year period (Figure 30–34) shows:

- There is a tendency to preserve the preoperatively established exocrine function in the postoperative period;
- Within the framework of the study, anastomosed patients, undergoing pancreatogastroanastomosis demonstrate a lower relative proportion of patients with severe exocrine insufficiency compared to those with pancreatojejunoanastomosis;
- There is a tendency to maintain lower mortality rates in the PGA group;
- There is a strong correlation ($r = 0.568$; $p = 0.001$) between mortality and exocrine insufficiency in the study groups.

For the purposes of the study, the impact of exocrine function on postoperative weight loss and performance of patients with PA was investigated. The statistics outline the following dependencies:

Table 32. Dependence of performance status (PS = 3–4) of patients with PA on postoperative exocrine capacity

	Честота	**Процент**
FE-1 < 100	46	63,9
FE-1 > 100 μg/g	32	36,1

Postoperatively, 63.9% of patients with PS = 3 and 4 had FE-1 levels below 100 μg/g. There is a tendency to decrease the influence of exocrine function on PS, although in most patients poor performance status remains associated with exocrine insufficiency (Table 32).

Table 33. Postoperative proportion of patients with clinically significant weight reduction

	Честота	Процент
Редукция на тегло	44	64,7
Контролна група	24	35,3

The postoperative relative share of patients with weight reduction significantly decreased to 64.7% of those studied (Table 33). This fact is probably due to a complex of reasons. On the one hand, there is restored patency of the main pancreatic duct, which is a prerequisite for improved function of the pancreatic remnant. Another possible cause could be the resection of the primary tumor causing cancerous cachexia.

Table 34. Dynamics in months of patients with postoperative weight loss

Месец	Честота	Процент
1	2	2,9
2	8	11,8
3	12	17,6
4	12	17,6
5	4	5,9
6	4	5,9
7	10	14,7
8	4	5,9
9	2	2,9
10	2	2,9
11	2	2,9
12	2	2,9
13	4	5,9

Table 34 presents the significant time intervals with regard to the indicator of weight loss during the months of follow-up. The table shows that the highest percentage of those surveyed lose significantly ($t = 2.884$; $p = 0.001$) their weight in the third, fourth and seventh months. Weight loss in months 3 and 4 is likely due to the occlusion of the pancreatic duct from gastric mucosa in the pancreatogastroanastomosis group during this time interval, resulting in severe exocrine insufficiency and indigestion. Another possible factor in this time interval is atrophy of the residual pancreas as a result of postoperative complications or other pathophysiological mechanisms associated with dysregulation of pancreatic secretion and altered topography of the digestive organs as a result of surgery. The percentage increase in patients with weight reduction in the 7th postoperative month is largely due to the impetus of cancer.

Additionally, the possibility of using the diameter of the main pancreatic canal as a criterion for exocrine competence of the pancreas has been investigated. The statistics showed the following results:

Table 35. Exocrine function of the pancreas postoperatively with a size of the main pancreatic canal of more than 3 mm

	Честота	**Процент**
FE-1 < 200	46	74,2
FE-1 > 200 μg/g	16	25,8

This tendency significantly decreases postoperatively (Table 35), probably due to the removal of the tumor formation that disrupts the patency of the pancreatic duct. In this way, it becomes possible to incorporate the enzymes secreted by the pancreatic residium into the digestion process. Despite these trends, the results show that in both cases, the size of the pancreatic duct can serve as a reliable guide for pancreatic exocrine function.

When monitoring exocrine pancreatic function in patients with pancreatic fibrosis, statistical analysis showed the following relationship:

Table 36. Exocrine postoperative function in patients with pancreatic fibrosis

	Честота	Процент
FE-1 < 200	42	80,8
FE-1 > 200 μg/g	10	19,2

The tendency to impaired exocrine function in fibrotic pancreas, observed preoperatively, persisted after surgery (Table 36). The increase in percentage of patients with pancreatic fibrosis and moderate exocrine insufficiency is probably due to the recanalization of the common pancreatic duct, which is a necessary and mandatory condition for the normal digestive process. The group of patients with improved indicators of pancreatic digestive function showed better pancreatic reserve preoperatively.

5.7. INFLUENCE OF EXOCRINE FUNCTION ON THE INCIDENCE OF METACHRONIC METASTASES AND LOCAL RECURRENCES

For the purposes of the study, a scan control was carried out for metastases and recurrences of the contingent during the 4th postoperative month. The time range has been selected with a view to optimal survival during this period. The exocrine function of patients with disease progression was analyzed in order to test the hypothesis of the influence of exocrine function on the possibility of stroma formation in pancreatic adenocarcinoma.

During the study, a statistically significant increase in the incidence of hematogenous metastasis and local recurrence was found in patients with severe exocrine insufficiency compared to the groups with moderate insufficiency and normal function of the pancreatic residue.

The control CT scans performed in the fourth postoperative month found:

- In two of the patients studied (2.17%; n = 2/18), pulmonary metastases of hematogenous appearance were registered (Figure 35);

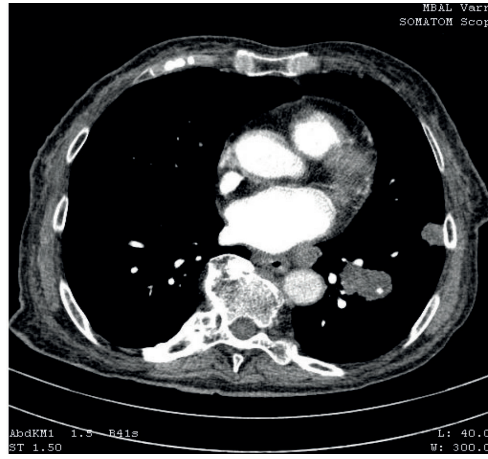


Figure 35. Patient with metachronic metastases in the left lung lobe, registered in the fourth postoperative month

- In eight of the cases (8.69%; n = 8/18), a scan spread of the process in the liver parenchyma was detected (Figure 36);

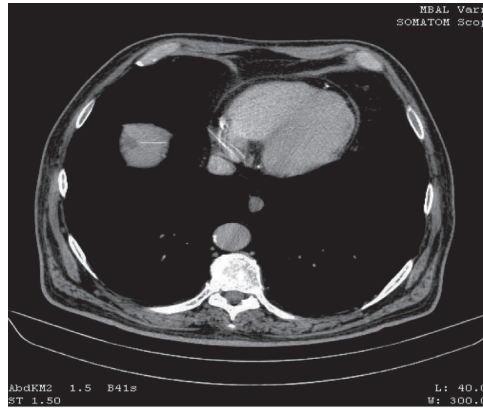


Figure 36. Patient with metachronic liver metastasis

- Eight of the patients studied (8.69%; n = 8/18) showed a local recurrence of the pancreatic neoplasm;

Progression of the disease during the one-year follow-up period was reported in 39.13%.

Table 37. Disease progression (metastasis and local recurrence) in patients with FE-1 levels < 100 μg/g

	Честота	Процент
Прогресия на заболяването	32	71,6
Стациониране на процеса	14	30,4

The statistical analysis of the results obtained (Table 37) shows that 71.6% of the studied patients with severe exocrine insufficiency have progression of cancer within the follow-up period. These results were compared with data from the studied patients with moderate exocrine insufficiency and normal digestive function.

Table 38. Disease progression (metastasis and local recurrence) in patients with FE-1 levels > 100 μg/g

	Честота	Процент
Прогресия на заболяването	28	56,9
Стациониране на процеса	18	39,1

In the studied group with moderate exocrine insufficiency and normal function of the residual pancreatic parenchyma, disease progression was observed in 56.9% of cases (Table 38). These results show a statistically significant difference in the progression of the neoplastic process in the two compared groups and make it clinically possible to hypothesize the deterrent effect of normal digestive function on the spread of PA.

5.8. POSTOPERATIVE SURVIVAL OF PATIENTS WITH PANCREATIC ADENOCARCINOMA

For the purposes of the study, survival in patients with severe exocrine insufficiency was analyzed. At the same time, the indicator in the group with moderate exocrine insufficiency and normal residual gland function is examined. Statistically, the survival factor for both types of anastomotic techniques was also tracked. The study identified several factors contributing to a statistically substantiated significant increase in survival and improvement in the quality of life of patients who underwent pancreatic duodenal resection for pancreatic adenocarcinoma.

Table 39. A

Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
VAR00001	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
ПИА	8,067	,530	7,029	9,105	7,000	,433	6,151	7,849
ПГА	9,966	,638	8,716	11,216	8,000	,663	6,700	9,300
Overall	9,053	,424	8,222	9,884	8,000	,397	7,221	8,779

Estimation is limited to the largest survival time if it is censored.

Table 39. B

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6,828	1	,009
Breslow (Generalized Wilcoxon)	4,505	1	,034

The vector of trend weights is -1, 1. This is the default.

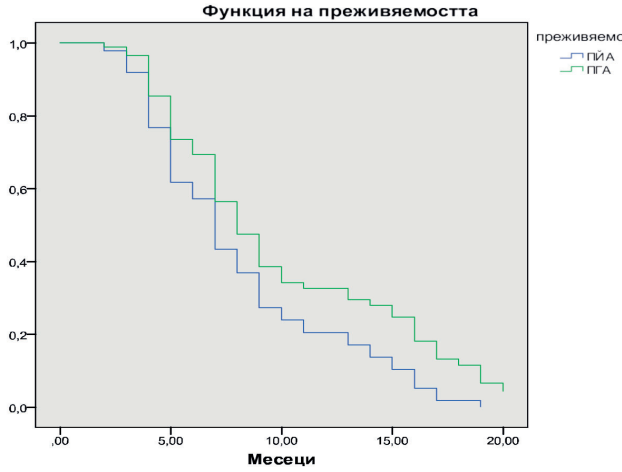


Figure 37. Table 39 A and B Survival analysis of the two types of anastomotic techniques compared in the study

Figure 37 shows the systematic course of the processes in patients undergoing pancreatogastro- and pancreatojejunoanastomosis, as well as the point grouping of peaks in survival.

Survival is measured in months. The median survival rate for patients with PGA is 9,966 and for those who have suffered PGA is 8,067. Regardless of the seemingly similar results, a statistically significant difference is reported on both coefficients from the analysis Log Rank (Mantel-Cox) and Breslow (Generalized Wilcoxon) respectively Sig. 009 & .034

The results give reason to think in several directions:

1. A lower number of detected postoperative complications of type C (ISGPS) in the pancreatogastroanastomosis group is associated with improved survival;
2. The tendency observed in the study to maintain moderate exocrine insufficiency in the PGA-group leads to stationary development of the neoplastic process by means of a VDR-mechanism. For more in-depth conclusions regarding the differences in survival and exocrine insufficiency, two other analyses were made using the reconstructive techniques used.

Table 40. A

Means and Medians for Survival Time								
	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Тежка екзокринна недостатъчност	6,859	,301	6,270	7,448	7,000	,558	5,906	8,094
С налична екзокринна функция (FE1>100 µg/g)	9,354	,442	8,488	10,220	9,000	,364	8,287	9,713
Overall	8,180	,307	7,579	8,781	8,000	,458	7,102	8,898

a. Estimation is limited to the largest survival time if it is censored.

Table 40. B

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	13,097	1	,000
Breslow (Generalized Wilcoxon)	12,292	1	,000

Test of equality of survival distributions for the different levels of VAR00001.

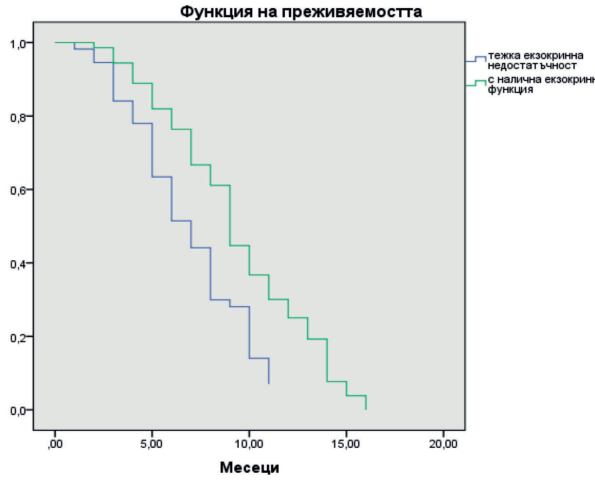


Figure 38. Table 40. A and B. Survival Analysis in Patients Who Have Undergone PJA with Severe Exocrine Insufficiency and Present Exocrine Function

The statistical results from Figure 38 show that in patients undergoing pancreatojejunoanastomosis, there is a statistically significant difference in the survival parameter in the group with severe exocrine insufficiency (cf. 6,859) and the one with preserved exocrine function (FE-1 over 100 micrograms) (cf. 9,354). These data also correspond to trends in the available literature in terms of survival. An interesting fact is the significant and visible difference in terms of the factor of exocrine pancreatic competence. Apparently, this study also found that it is a parameter of serious importance in terms of survival in terms of its ability to block the development of stroma in this type of neoplasm.

Table 41. A

Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
1,00	7,235	,386	6,478	7,991	7,000	,558	5,906	8,094
2,00	9,370	,443	8,460	10,198	9,000	,399	8,218	9,782
Overall	8,243	,313	7,629	8,857	8,000	,458	7,102	8,898

a. Estimation is limited to the largest survival time if it is censored.

Table 41. B

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	8,700	1	,003
Breslow (Generalized Wilcoxon)	11,008	1	,001

Test of equality of survival distributions for the different levels of VAR00001.

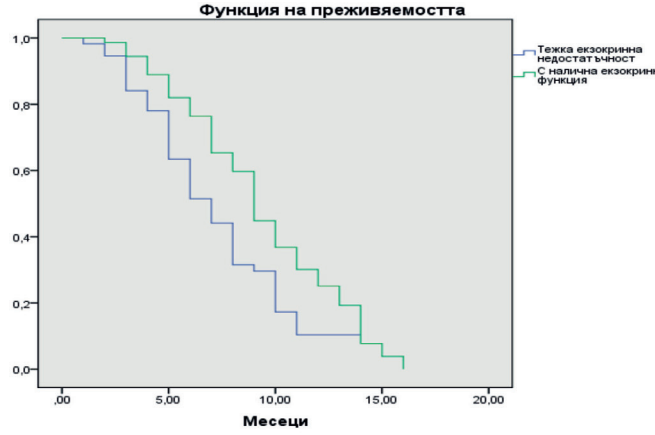


Figure 39. Table 41. A and B Survival Analysis in Patients Undergoing PGA with Severe Exocrine Insufficiency and Present Exocrine Function (FE-1 > 100 μg/g)

In the next analysis (Figure 39), a similar trend with a high degree of significance was again observed in patients undergoing pancreatogastroanasis. In PGA, however, the average survival in conditions of severe exocrine insufficiency is significantly higher than in PJA (cf. 7,235).

During the statistical analysis (Table 42), it was found that the mechanical icter preoperatively can be distinguished as an independent factor affecting the life expectancy of patients with PA included in the study.

Table 42.Survival in patients with preoperative icter compared to the control group of patients

	Без иктер	**С иктер**
Брой	16	76
Средно	6,1053	5,6250
Стандартно отклонение	3,39944	4,13824
Минимално	2,00	1,00
Максимално	14,00	12,00

The dissipation from the mean in ICTER patients is greater due to a higher proportion of random factors such as an increased proportion of significant postoperative complications (ISGPS) in this study group, as well as a high proportion of patients with cholangitis preoperatively. Statistics show that patients without mechanical jaundice demonstrate better survival relative to icteric jaundice, despite the comparable TNM and G stages of the compared groups.

For the purposes of the study, a comparative analysis of the groups with moderate exocrine insufficiency and those with normal exocrine function was carried out in relation to the survival factor:

Table 43. A

Paired Samples Statistics

	Средно	Брой	Стандартно отклонение	Средна стандартна грешка
FE-1 > 200	8,2000	10	3,96232	1,77200
FE-1 = 100–200	5,8000	10	4,76445	2,13073

Table 43. B

Paired Samples Correlations

	Брой	Корелация	Значимост
FE-1>200 &	10	-,871	,054

Таблица 43. C

Paired Samples Test

	Средно	Стандартно отклонение	t	Значимост (2-tailed)
FE-1>200 & FE-1 = 100–200	2,40000	8,44393	,636	,560

The T-test performed (Table 43 A; B and C) indicates a trend of difference in survival factor in the groups with normal exocrine function assigned to those with moderate digestive insufficiency. Despite the noted trend, there was no statistically significant difference in survival in the two compared samples of patients. These results correlate with the conclusions of numerous prospective randomized trials showing the sufficient availability of 10% of the secretory capacity of the gland to maintain its digestive function. This statistical analysis once again confirms the effect of malnutrition in this type of neoplasm on patient survival related to the characteristic effects of hypovitaminosis on the initiation and development of pancreatic adenocarcinoma.

6. DISCUSSION

6.1. DESCRIPTIVE CHARACTERISTICS

The average age of prevalence of pancreatic adenocarcinoma in epidemiological studies shows the highest incidence of the disease in the age range between fifty-five and seven–ten years [41,151]. According to this indicator, the data from the National Cancer Registry do not show a statistically significant deviation, and the age interval in which the disease manifests itself most often is 60–79 years [4]. The distribution of patients in the current study shows a similar peak in the prevalence of pancreatic adenocarcinoma in the age range between 65 and 73 years. By this parameter, the sample in the study does not give a statistically significant deviation from the results obtained from the literature review.

The gender distribution of PA patients in the global database shows male involvement between 1.7 and 7.5% of cases. Women with proven pancreatic adenocarcinoma are in the range of 1.4–5.1%. These data demonstrate a small difference in the sex prevalence of the disease [43]. The data of the National Cancer Registry shows the ratio of men to women with PA, 3.9% to 4.9% [4], which does not differ statistically from the distribution of the indicator worldwide. This study shows a statistically similar balance in terms of the demographic indicator gender. The data in the study showed an incidence among women – n = 50 (54.3%), close to that in male patients – n = 42 (45.7%). The latter fact confirms that there is a statistically insignificant difference in the sex distribution of the disease in the Bulgarian population. However, there is a more common incidence of pancreatic cancer among women.

6.2. CLINICAL MANIFESTATIONS

Mechanical icter. The incidence of mechanical icter as the first manifestation of pancreatic head carcinoma, according to literary searches, is on average 80% [97]. The current study showed that 82.60% of the sample sought medical attention due to yellowing of the skin and sclera. On the basis of mechanical jaundice, diagnostics were carried out and adenocarcinoma of the pancreatic head was found in 74.4%. Ictera is perceived as a late symptom, indicating a locally advanced disease. These data testify to the late diagnosis of pancreatic adenocarcinoma both in the study and worldwide. Additional tests are needed in order to develop an effective screening for the prevention of the disease. The study shows that 30% of the studied cases with mechanical icter and borderline resectability underwent bile drainage in other hospitals. The European and American Consensus on Pancreatic Adenocarcinoma recommend bile drainage preoperatively only for patients undergoing neoadjuvant chemotherapy, cholangitis clinic, and severe symptomatic icter [70, 156, 232]. The reasons for the consensus are that preoperative bile drainage worsens postoperative outcomes and increases morbidity in these patients. This fact is confirmed by the statistical results of the study, showing a 70% incidence of cholangitis among stented patients. It would be appropriate to use consensus criteria (NCCN and ESMO) in all hospital settings before undertaking bile duct stenting. The current study outlines cholangitis as a stand-alone risk factor for postoperative complications after PD. The latter finding is related to the effect of complications on the exocrine function of the pancreatic residum in the study.

Chronic pancreatitis. The analysis of the literature demonstrates a low incidence of acute pancreatitis as a clinical manifestation of pancreatic adenocarcinoma [136]. A literature review found that the incidence of malignancy in patients with chronic pancreatitis reached 4% after the twentieth year of disease [106, 141, 254]. Chronic pancreatitis with a duration of more than 5 years is reported by most authors as an initiating factor of neo-oncogenesis.

In the present study, the incidence of diagnosed chronic pancreatitis upon admission of the patient to the surgical unit was established in 19.2% of cases with histologically verified postoperatively. In fact, chronic pancreatitis is 60.5% of the studied cases. This dissonance in the data is assumed to be due to a moderate PEI in this study sample. These patients did not have a complete clinical manifestation and were not diagnosed in a timely manner. The large proportion of patients with underlying chronic pancreatitis and PA in the study speaks in favor of the neo-oncogenesis-initiating role of the inflammatory process. However, one should not ignore the fact that pancreatic neoplasms, on the other hand, often cause occlusion of the main pancreatic duct and the development of chronic pancreatitis. In the group with pathomorphologically intact pancreas, the characteristic gene mutations causing the development of PA and familial pancreatic cancer are likely to affect.

Impaired exocrine function preoperatively

Monitoring the frequency of preoperative disorders of exocrine function aims to assess its attitude to the occurrence of pancreatic neoplasms and the effects of PD and PPPD with the reconstructive techniques used on this parameter. A literature review aimed at establishing the incidence of exocrine insufficiency preoperatively in patients with PA showed a PEI margin of between 22 and 76% [140, 154]. The current study demonstrated a preoperative incidence of moderate to severe exocrine insufficiency (FE-1 < 200 μg/g) in 69.6% of cases. This result is probably related to the large proportion of patients with underlying chronic pancreatitis and occlusion of the main canal of the pancreas in the study. Clinically pronounced maldigestion was observed in 80.8% of patients with FE-1 levels < 200 μg/g. This indicates the presence of symptoms among cases of moderate exocrine insufficiency.

Weight reduction. Weight loss in patients with pancreatic adenocarcinoma is due to many factors with mutual influence, mainly due to cancerous cachexia and exocrine insufficiency. Literature sources show an average incidence of cachexia over 80%, defined as a loss of more than 10% of

body mass within six months [183]. The study found cachexia in 73.91% of cases. This symptom was additionally combined with exocrine insufficiency in 56 patients. Thus, the two causes of weight reduction occur among 82.4% of those examined. A fecal elastase-1 limit of 100 μg/g was used here, thus comparing patients with severe exocrine insufficiency and patients with normal digestive function or moderate exocrine insufficiency. The latter indicates that digestive disorders are a leading factor causing cachexia in patients with PA. These data orient us in the relative share of factors leading to weight loss and poor performance of patients preoperatively. Additionally, weight loss preoperatively in patients undergoing PGA and PJA has been studied. In this way, the impact of the anastomotic technique on exocrine function is evaluated, by assessing the state of PEI preoperatively in both groups. In this study, preoperative significant weight loss was found in 62.50% of the PGA group compared to 37.50% of those reconstructed by PGA.

Impaired endocrine function

In the literature, diabetes mellitus is associated with an increased risk of pancreatic adenocarcinoma. Association of diabetes mellitus to the occurrence of the neoplasm was observed in 9.7% of cases [31, 105, 150, 155, 181, 194, 216]. The study found diabetes mellitus in n = 46 (53.5%) of patients preoperatively. The prevalence of insulin-dependent diabetes among the group of patients with chronic pancreatitis was further studied. It was found that 46.2% of the examined patients with chronic pancreatitis are diabetics. In this way, patients with combined pancreatic insufficiency are differentiated. These results stratified patients with poor pancreatic reserve in the study.

Performance status preoperatively. The study of this indicator in the study aims to determine the dependence of PS on exocrine function. The question facing the study is to what extent this indicator is influenced by the oncological process. Performance status predetermines the choice of chemotherapy regimen [58], as well as the possibility of performing radical surgical intervention. The current study analyzed patients with PS = 3

and 4, comparing this indicator with FE-1 levels below 100 μg/g. It was found that patients with "poor" performance status had severe exocrine insufficiency in 83.3% of cases. This result showed the relationship of maldigestion with the condition of patients with PA, which reflects on both their surgical and chemotherapy effects.

6.3. IMAGING

One of the radiological criteria for chronic pancreatitis in the literature is a pancreatic duct size greater than 3 mm [59, 71]. In this study, the correlation between this indicator and the presence of exocrine insufficiency was traced. As a result of the analysis, it was found that 96.8% of patients with a pancreatic canal diameter of more than 3 mm preoperatively had fecal elastase levels below two hundred micrograms per gram. This result makes it possible to predict the exocrine function by measuring the main pancreatic duct. The ratio of the consistency of the pancreatic parenchyma to an enlarged pancreatic canal of more than 3 mm was further studied. In 74.2% of the studied cases with dilated ductus versungianus, a "hard" pancreas was found, and the subjective experience of the surgeon here would affect the statistical results. The pancreatic texture could be used to determine the exocrine capacity of the gland and the possibility of improved function, postoperatively due to the release of the pancreatic duct compressed by the tumor formation. The level of exocrine function was monitored in patients with scan atrophy of the organ. The studied patients with perilobular fibrosis, reduced parenchymal thickness and calcifications had fecal elastase levels below 100 μg/g in 88.5% of cases. A correlation analysis was performed between the scan data for fibrosis, atrophy, calcifications, dilated main pancreatic duct and the intraoperative assessment of the "hard" pancreas indicator. A very strong correlation was found between the studied parameters ($r = 0.916$; $p < 0.001$). The results show that with a high degree of reliability, the intraoperative assessment of the consistency of the pancreas overlaps with the results of imaging diagnostics. The statistical results give freedom of substitutability to laboratory, scan and subjective

surgical methods for assessing exocrine function. In addition, they allow orientation when performing the diagnostic protocol for the pancreas, for the type of appropriate anastomotic technique. However, these results were not obtained in a prospective randomised trial and should be taken with some reservations. It is advisable to conduct a similar multiplanar study in the future with a greater degree of evidence.

In order to further investigate the effect of the anastomotic technique on the exocrine function, the circumference of the main pancreatic canal was measured in the two anastomotic techniques used. The results were compared with the postoperative ones, and the aim was to establish to what extent the exocrine insufficiency is due to underlying chronic pancreatitis or occlusion of the pancreatic canal by the neoplasm and to what extent it is a consequence of the performed resection and anastomosis.

The statistical results give reason to consider a wider use of CT to determine preoperative exocrine function, which would also have prognostic significance in patients with pancreatic adenocarcinoma.

6.4. PERIOPERATIVE DETAILS

All patients included in the study underwent R0 resection and standard lymphatic dissection, thus ensuring an equal start of postoperative follow-up, the influence of complications and exocrine function on survival and mortality in the studied patients. The operative time, intraoperative blood loss and the operative technique correspond to the average permissible values.

Postoperative complications described in the literature vary widely. In general, morbidity after pancreatoduodenectomy ranges between 18 and 52%. [158, 198, 224 ,229, 231, 256] In particular, post-pancreatectomy fistula occurs in 3–45% [26, 27, 251, 257]; impaired gastric emptying was recorded on average in 17.3% of patients [159]; Post-pancreatectomy hemorrhage was observed in 5–12% of those studied in various sources [198]. Due to the still high morbidity and mortality after duodenopancreatic resection,

many authors investigate and compare the complications of the two main anastomotic techniques. A meta-analysis of randomized prospective trials showed that there was no statistically significant difference in the complication rates of the two reconstructive techniques [146, 155].

Numerous studies and meta-analyses outline the presence of a "soft" pancreatic texture preoperatively as an independent risk factor for the formation of a pancreatic fistula [10, 25, 29, 47, 87, 176, 197, 255], as well as the absence of underlying chronic pancreatitis [29].

The study further matched the texture of the pancreas with the reconstructive technique used. Pancreatogastroanastomosis was preferred in the case of a "soft" pancreas in 68.40% of cases to 26.60% in the case of a "hard" pancreatic texture. In 73.30% of cases, pancreatojejunoanastomosis was performed in conditions of fibrotic (hard) pancreas, and in other cases in conditions of normal pancreatic residue. These results show that in the study the anastomosis technique used is dependent on the individual preferences of the surgeons who performed the interventions. This fact allows for a more accurate statistical analysis of complications among those anastomosed by PGA and PIA due to the general opinion that PGA is safer in conditions of "soft" pancreas.

Prospective and randomized trials have shown a significantly increased incidence of severe postoperative complications (74% vs. 39%, $P < 0.001$), rehospitalization rates, and prolongation of hospital stay in patients undergoing ERCP for preoperative burdening of hyperbilirubinemia due to pancreatic head adenocarcinoma. The comparison was attributed to patients undergoing pancreatoduodenectomy under mechanical icter conditions [86, 232].

For the purposes of the study, the relationship of mechanical icter preoperatively to postoperative complications is further investigated. Statistical analysis demonstrated a frequency of complications after duodenopancreatic resection among icteric patients in the study in 92.1% of cases. All patients who developed fistula C in the study had obstructive jaundice preoperatively. These results are probably due to impaired hepatic synthe-

tase function, resulting in tissue edema and reduced repair in the area of anastomosis performed. Related to the share of postoperative hemorrhage that developed among the contingent of patients with mechanical icter, the cause is probably impaired hemostasiology along with other factors predisposing to the development of this type of complications. From the analysis performed, icter can be reliably identified as a risk factor for postoperative complications in the studied contingent of patients.

The current study tracked the incidence of severe complications among the group undergoing pancreatogastroanastomosis and those with pancreatojejunoanastomosis. Pancreatogastroanastomosis was performed in 63% of cases, and pancreatojejunoanastomosis in 37%. In the PGA group, intraluminal bleeding type C was observed in 4% of the examined, compared with extraluminal hemorrhage type C in the PJA group in 7%. Type B hemorrhage is not observed in patients with PGA reconstruction. In the group with PJA anastomosis, hemorrhage B is recorded in 14% of cases. In this study, a higher incidence of PPH was observed among patients with pancreatojejunoanastomosis. In those reconstructed by PGA, the hemorrhage is entirely intraluminal, with the source of the pancreatic residum. In conclusion, more careful processing of the residual pancreas and stitching of all vessels in the anastomosis area is imperative in order to reduce the incidence of this complication.

With regard to the development of postpancreatectomy fistula, the development of type C fistula is observed only among PJA reconstructed (7%). On the other hand, the proportion of type B fistula is twice as high in the PGA group (14%). Additionally, the frequency of intra-abdominal abscesses in both anastomotic techniques was studied, and in the PGA group the complication was in 18% of cases, compared to 7% of those undergoing pancreatojejunoanastomosis.

Impaired gastric emptying is observed with a twice higher share of 14% in the PGA group compared to 7% of patients with pancreatojejunoanastomosis.

In conclusion, the main types of postoperative complications are evenly distributed among the anastomotic techniques compared. However, severe class C complications (ISGPS) are more common among the studied patients undergoing pancreatojejunoanastomosis.

The incidence of complications associated with the type of anastomosis in the study was further analyzed according to the Dindo-Clavien classification. Here, too, statistical analysis showed a higher proportion of severe complications (16%) among patients reconstructed by PJA, compared to 4% in the PGA group. The results are based on a retrospective cohort study. It is recommended, on the basis of randomized prospective studies, to compare in detail the degrees of complications after duodenopancreatic resection, based on the anastomotic technique used.

The incidence of acute postoperative pancreatitis with both anastomotic techniques was studied. This complication, according to the reviewed literature sources, leads to fibrosis of the pancreas and impaired exocrine function. This complication in the study occurs with twice the frequency in PGA type reconstruction. A probable cause of this complication is the devascularization of the pancreatic residum along 3 cm and the impaired collateral network during the destructive part of the intervention. These putative pathogenetic mechanisms could be the subject of a more in-depth study with the aim of reducing the incidence of this complication due to its relationship to quality of life and survival.

6.5. EXOCRINE FUNCTION AFTER DUODENOPANCREATIC RESECTION

As a result of a literature review of factors affecting exocrine function after duodenopancreatic resection, it was found that pancreatic fistulas lead to involution of the residual pancreas and hence to the deepening of exocrine insufficiency [66]. In order to analyze this problem in more detail, the study investigated the frequency of exocrine insufficiency among patients with fistula B and C. Patients with type B fistula in the studied contingent

of patients developed scanegraphic atrophy of the pancreas and exocrine insufficiency in 60% of cases. All patients with fistula C studied demonstrated these manifestations. This result shows almost twice the share of patients who developed exocrine insufficiency after type C fistula, which distinguishes this complication as a risk factor for postoperative exocrine failure among the examined.

The literature analysis demonstrates as one of the leading causes of post-pancreatectomy exocrine insufficiency preoperative obstruction of the main pancreatic duct and the underlying chronic pancreatitis. The surgical intervention itself disrupts multiple mechanisms regulating the secretion of the pancreas, including extensive denervation of the compartment. At the same time, there is a loss of pancreatic parenchyma. Postoperative effects on these processes are exerted by pancreatic fistulas, postoperative pancreatitis, intraanastomotic blockage of the pancreatic canal [66,195]. In cases undergoing pancreatogastroanasis, the buffering properties of the food favor the action of pancreatic enzymes, and this effect is potentiated in the case of pylor-sparing surgery [118]. Pancreatojejunoanastomosis, due to negative feedback from a high-calorie jejunal load, lowers exocrine secretion and, as a consequence, creates conditions for maldigestion [214]. Another factor affecting exocrine function is the presence of trophic stimuli for the pancreas from the duodenum, which are conserved in PPPD [104].

The study analyzed the exocrine function preoperatively and after the intervention in both groups of anastomotic techniques. Statistical analysis showed a general tendency to maintain indicators of exocrine pancreatic function postoperatively. Preoperative exocrine insufficiency was found in n = 64 (69.6%) of the examined. Postoperative digestive failure was recorded in n = 56 (60.9%) of the patient contingent. These results are probably due to underlying chronic pancreatitis and basally depleted secretory reserve of the gland. Pancreatic duct deobstruction postoperatively does not lead to complete normalization of pancreatic function.

The examined patients undergoing pancreatogastroanastomosis were fibroscopically monitored in order to assess the condition of the main pan-

creatic canal and to establish the cases of anastomosis covering by the gastric mucosa. Statistical analysis showed that 35.7% (n = 20) of those reconstructed by PGA had anastomosis occlusion. There is a strong correlation (r = 0.678; p = 0.001) between mucosal occlusion in the first/second postoperative month and FE-1 levels below 100 μg/g. if patients with mucosal blockage of the pancreatic canal are excluded in the group with performed PGA. These data make sense of a more in-depth analysis of the effect of fibrogastroscopic resection of this section of the gastric mucosa on digestive function, as well as to track the consolidation of this effect over time.

The possibility of using the diameter of the main pancreatic canal in postoperative imaging diagnostics was investigated according to the recommendations for pancreatic adenocarcinoma for determining exocrine capacity. A reduced correlation between a canal diameter of more than 3 mm and digestive failure was found. This is probably due to its release after removal of the tumor formation against the background of partially preserved secretory capacity. In conclusion, the postoperative sensitivity of this indicator remains 74.2% and can be used to assess exocrine function.

Additionally, the influence of pancreatic fibrosis on exocrine insufficiency in the postoperative period is investigated, establishing the preservation of this correlation. There is an increase in the percentage of patients with sclerosis of the pancreatic residue and moderate exocrine insufficiency. This outlined trend in the study is probably due to deobstruction of the main pancreatic duct and partially preserved secretory function of the gland.

A retrospective analysis in the literature tracking preoperative and postoperative levels of FE-1 in the third month, first and second year demonstrated normal levels of the indicator in 78% of cases preoperatively. In the third month, reduced levels of FE-1 were found in 48% of those tested. In the first and second years, patients with exocrine insufficiency detected by fecal elastase-1 examination were 73% and 50% [154].

The previous study did not report a group with moderate exocrine insufficiency and one with severe insufficiency. The follow-up of exocrine

function in the present study is in the first, second, third and twelfth postoperative months. On the thirtieth postoperative day, severe exocrine insufficiency, with FE-1 levels below 100 μg/g, was demonstrated by 21.70% of patients undergoing pancreatogastroanastomosis and 15.20% of patients with pancreatojejunoanastomosis. Moderate maldigestion was observed in 17.40% of patients with PGA and 6.50% of the PIA group. Postoperative deterioration of exocrine function in the first month was found in 12% of those who underwent PGA and in 25.2% of cases with PIA. The pancreatogastroanastomosis group showed a tendency to preserve exocrine function compared to preoperative levels. In the second month, there is a tendency towards deepening of disorders in exocrine function and an increase in the number of people tested with moderate exocrine insufficiency. The number of patients with normal FE-1 values among those reconstructed by PGA was maintained, and decreased by 10.9% in the PIA group. During the third postoperative month, statistics indicate the stationing of the three levels of exocrine function in patients with pancreatogastroanastomosis. In the PJA group, a decrease in the number of patients with severe enzyme deficiency is outlined, reaching 15.20%. 14.47% of those examined remain with normal pancreatic function. In the first year, there was no severe exocrine insufficiency among the two groups compared. These data speak of a lack of twelfth-month survival in patients with FE-1 levels below 100 micrograms per gram. Moderate exocrine insufficiency was observed at twice the rate in the PJA sample in the first year. In summary, within the framework of the study, pancreatogastro-anastomoses showed a lower relative proportion of patients with severe exocrine insufficiency compared to the control group.

The study compared mortality in the one-year period with digestive pancreatic capacity. The results showed lower mortality rates in the PGA group. A strong correlation between mortality and severe exocrine insufficiency has been established. These data, compared with the literature study, clinically confirm the results of experimental models demonstrating the pathogenetic chain: impaired absorption of vitamin “D” – pronounced tumor stromal reaction (due to lack of active VDRs, generalization of the process and/or recurrence). The latter should be the subject of prospective randomized

clinical trials, which would contribute to complex treatment and improvement of the results of therapy of this type of neoplasms.

This direction of the study was further developed with the monitoring of metastasis and recurrence of pancreatic adenocarcinoma in the context of the exocrine function of the pancreas. The study aims to test the hypothesis of the negative influence of normal digestive function, in particular vit. D, on the ability of the PA to form a stroma. The exocrine function in the 4th postoperative month was statistically analyzed among patients with hematogenous metastases and relapses. It was found that in 71.6% of the cases of generalization of the process, patients had evidence of severe exocrine insufficiency. The results were compared with those of patients with moderate exocrine insufficiency and normal function. In the last two groups, progression of the disease was recorded in 56.9% of cases. In conclusion, the current results should be verified in a randomized prospective study. This would lead to a deeper understanding of the biology of PA and improve its multimodal treatment.

Weight reduction, along with all the negative effects of impaired digestive function, in conditions of pancreatic adenocarcinoma, greatly affects the physical parameters of quality of life, performance status and survival. What has been said so far puts this indicator in one of the leading and clinically significant positions in this disease. In terms of weight consumption, the results of the study show a significant decrease in the number of patients with this symptomatology postoperatively (64.7%). There are two probable reasons leading to this result. On the one hand, pancreatic exocrine function was improved by releasing enzymatic drainage, on the other hand, the primary tumor causing cancerous cachexia was removed. The highest proportion of patients with significant weight loss was recorded in the third, fourth and seventh postoperative months. At months 3 and 4, it was probably due to severe exocrine insufficiency due to mucosal obstruction of the pancreatic canal in some of these patients (PGA). Another cause is pancreatic atrophy and fibrosis, as a consequence of postoperative complications. In the 7th postoperative month, the reduction of body mass is mainly associated with an impetus of cancer.

Postoperatively, the performance status as a function of exocrine activity was monitored. The results showed "poor" PS (score 3–4) in 63.9% of cases with fecal elastase levels below 100 μg/g. These data demonstrate a lower dependence of performance status on severe exocrine insufficiency compared to that in the preoperative period (83.3%). This is probably due to the intervention of many factors affecting this indicator.

In the context of the influence of exocrine function on pancreatic adenocarcinoma, the literature is further examined. A prospective randomized trial showed a correlation between FE-1 levels and survival. This study showed twice the survival rate among patients with normal exocrine function and pancreatic adenocarcinoma [175].

The current study tracked survival among patients with severe, moderate exocrine insufficiency and normal pancreatic function. Survival in this study was measured in months, as opposed to the standard intervals for oncological diseases, due to the low values of this indicator characteristic of the neoplasm. In many studies, the parameter of postoperative survival of patients with pancreatic adenocarcinoma is measured in months.

Patients undergoing pancreatogastroanastomosis showed an average survival of 9,966 months, compared to 8,067 months in patients with pancreatojejunoanastomosis. Probably this statistically significant difference in both coefficients, from the analysis -Log Rank (Mantel-Cox) and Breslow (Generalized Wilcoxon) respectively Sig.. 009 and 034 is due to the relatively small number of class C complications in the PGA group. Another partially related cause is the propensity of patients with PGA reconstruction observed in the study to maintain moderate exocrine insufficiency. The VDR mechanism for stationing tumor progression is probably related here. Those anastomosed by PJA showed a statistically significant difference in survival in conditions of severe exocrine insufficiency (6,859) compared to those with preserved digestive function (9,354). In patients undergoing pancreatogastronomosis, a similar difference in survival was observed between patients with and without exocrine insufficiency. Patients with enzyme insufficiency reconstructed by PGA showed significantly higher

survival compared to those who underwent pancreatojejunoanastomosis (cf. 7,235).

Additionally, in the present study, a T-test of the survival factor was performed in the group with normal exocrine function and the group with moderate insufficiency. Despite the trend, the statistical result does not report a significant difference in survival between the two groups. These results correlate with the available literature. Exocrine insufficiency has been defined in the following studies, with a deficiency of the enzymes trypsin and lipase with more than 90% of the norm, which corresponds to severe and clinically manifested exocrine insufficiency [195].

As an independent factor influencing the survival in the studied contingent of patients, the preoperative mechanical icter was distinguished. The study demonstrated better survival among ancteric patients, despite the comparable TNM and G stages. Statistical analysis demonstrated greater scattering than average among patients with mechanical jaundice. This is probably due to the higher proportion of random factors, such as clinically significant complications (ISGPS), the development of cholangitis, etc.

The comparison of the exocrine function and the individual degrees of its disorders with the indicators of mortality, survival and progression of the process, as well as the exclusion of the independent factors influencing these parameters that have emerged in the study, has not been carried out so far in such a multiplanarity. Due to the nature of the study, the results may be subject to some correction and reconfirmation after randomized prospective ones.

The study demonstrated, despite the results of the literature review, the essential importance of the reconstructive technique used in terms of severe postoperative complications, pronounced exocrine insufficiency, extended hospital stay, postoperative weight loss and performance status, survival and mortality. In terms of these indicators, pancreatogastroanastomosis showed better results in the study.

7. CONCLUSIONS

- The imaging diagnostic criteria for chronic pancreatitis and the intraoperative consistency of the gland show with a high degree of certainty the exocrine capacity of the pancreas. They could be used alone to detect digestive failure in patients with pancreatic adenocarcinoma.
- It is recommended to perform a control gastroscopy after pancreatogastroanasis is performed, due to the tendency to cover the anastomotic surface of the gastric mucosa. Mucosal incision in these cases could improve postoperative exocrine function.
- Pancreatogastroanastomosis shows a lower proportion of severe postoperative complications compared to pancreatojejunoanastomosis. Patients who have undergone such reconstruction have a shorter hospital stay, demonstrate good exocrine function, improved survival and quality of life.
- Preoperative mechanical icter appears to be an independent factor with a negative impact on the survival of patients with pancreatic adenocarcinoma.
- There is a statistically significant difference in the progression of the oncological process among patients with severe exocrine insufficiency compared to those with existing digestive function. Metastasis and recurrence are more common in the group with fecal elastase levels below one hundred micrograms per gram.
- Preserved exocrine function after duodenopancreatic resection for pancreatic adenocarcinoma leads to improved survival and lower mortality rates.

8. CONCLUSION

Exocrine function in the context of pancreatic adenocarcinoma is of utmost importance in many directions. Digestive competence leads to an improvement in performance status, maintenance of body weight and quality of life. In addition, patients with normal digestion show a lower incidence of recurrence and metastasis, prolonged survival and reduced mortality. All resectable patients with mechanical icter should undergo radical intervention, without preoperative biliary drainage. Encumberment of the bile ducts before pancreatoduodenectomy leads to an increased incidence of postoperative complications and generally lower survival.

In all possible cases, a pylor-sparing surgical procedure should be preferred. This method leads to good results in terms of the exocrine function of the pancreas.

The choice of reconstruction technique should be made strictly individually, specifying the degree of pancreatic fibrosis before the intervention through imaging diagnostics and intraoperatively through the tactile sense of the operator. In this way, the incidence of postoperative complications could be optimized and further deterioration of the functions of the residual pancreas could be avoided. Taking these actions would lead to an improvement in the parameters of quality of life, performance status and life expectancy. In addition, an improvement in parameters such as early postoperative mortality, duration of resuscitation and hospital stay. This would also favor the financial aspects of the treatment of this pathology.

As part of the complex treatment of pancreatic adenococinoma, it should be administered routinely, after determining the levels of fecal elastase, enzyme substitution therapy.

9. CONTRIBUTIONS

1. Dynamic monitoring of exocrine function in established reconstructions after pancreaticoduodenectomy, additionally demonstrating the impact of complications according to ISGPS on the functional fitness of the residual pancreas. Determination of the frequency of covering the pancreaticogastroanastomosis with gastric mucosa and the impact on exocrine secretion, as an option for screening monitoring and fiberscopic influence on this indicator.
2. Determination of the diagnostic value of indirect criteria for assessing pancreatic function in patients with PA.
3. Investigation of the impact of maldigestion on the tendency of pancreatic adenocarcinoma to systemic spread.
4. Monitoring the relationship of the functional fitness of the pancreas to the physical parameters of the quality of life after duodeno-pancreatic resection.
5. Analysis of survival as a function of pancreatic exocrine activity and identification of factors affecting postoperative survival of patients with pancreatic adenocarcinoma..

10. PUBLICATIONS RELATED TO THE DISSERTATION

1. Nikolov N, Sapundzhieva M, Pacholova Y. Causes and consequences of exocrine insufficiency after duodenopancreatic resection due to neoplasms. Journal of Military Medicine, ISSN-1312–2746 2021(3): 39–41.
2. Nikolov N, Sapundzhieva M, Pacholova Y. Advantages and disadvantages of pancreatic anastomoses after duodenopancreatic resection. Journal of Military Medicine, ISSN 1312–2746 2021(3): 36–38.
3. Nikolov N, Sapundzhieva M, Pacholova Y. Factors indicating a significant impact on survival in patients with adenocarcinoma of the pancreatic head. Journal of Military Medicine, ISSN-1312-2746 2021(4): 36-39.