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Results of surgical treatment of chronic pancreatitis with a high risk of developing pancreatic cancer

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Abstracts

Objective. To analyze the results of surgical treatment of patients with pancreatic insufficiency and a high risk of developing pancreatic cancer.

Materials and methods. The study included 39 patients treated in 2019–2023. In 20 (51%) patients, it was difficult to clearly differentiate between chronic pancreatitis and pancreatic cancer. In 19 (49%) patients, the diagnosis of chronic pancreatitis was not in doubt. All patients with complicated forms of chronic pancreatitis and suspected pancreatic tumor underwent a set of laboratory tests, and routine screening methods of instrumental diagnostics were used. In addition to standard methods of examination, the levels of matrix metalloproteinases and tissue inhibitor of metalloproteinases in the blood plasma were studied.

Results. The method of intraoperative multiple biopsy, improved by us, was an obligatory component of surgical care for a clear differential diagnosis of chronic pancreatitis and pancreatic cancer. In the presence of complicated chronic pancreatitis, during surgery, the biopsy was taken using a special punch instrument that resembles a pen, along the entire length of the main pancreatic duct along the upper and lower edges of the dissection in a checkerboard pattern. There were no complications of punch biopsy. Of the 20 patients in whom it was not possible to clearly differentiate between chronic pancreatitis and pancreatic cancer, 12 (60%) were diagnosed with diabetes mellitus. The characteristic changes in the pancreatic tissue gave grounds for performing extended resection interventions in these patients. In the remaining 8 (40%) patients without morphological changes inherent in malignancy, Whipple operation (2), longitudinal pancreaticoduodenectomy (2), Frey operation (2), and our proposed central pancreatic resection with preservation of the left anatomical segment (2) were performed. Drainage and resectional surgical interventions were performed in 19 (49%) patients with complicated forms of chronic pancreatitis. After radical surgical interventions for pancreatic cancer, 1 patient developed gastrostasis, and on the 11th day he underwent a relaparotomy with reconstruction of the gastroenteroanastomosis, and on the 30th day a subhepatic abscess was diagnosed in 1 patient, who underwent drainage with a subcostal mini–access with a positive effect. In 2 patients, after left–sided pancreatic resection, subdiaphragmatic abscesses were diagnosed on the left, they were treated minimally invasively with punctures and drainage under ultrasound control. Multiple organ failure occurred in 1 patient after surgery for internal pancreatic fistula, infected ascites as a complication of neglected chronic pancreatitis. The patient died. Infection of the median laparotomy wound occurred in 4 patients, and healing was achieved by controlled primary tension. Class B pancreatic fistulas occurred in 3 patients: 2 – after left–sided pancreatic resection, 1 – after longitudinal pancreaticoduodenostomy. In 1 patient, a class C permanent pancreatic fistula was formed after a combined (resection and drainage) intervention. Relaparotomy, subtotal resection with Roux–en–Y loop closure was performed.

Conclusions. Morphological changes in the pancreatic tissue in chronic pancreatitis in combination with diabetes mellitus, corresponding to the development of PanIN, are direct predictors of adenocarcinoma. Multiple intraoperative pancreatic biopsies are effective in verifying pancreatic malignancy. Pre– and intraoperative diagnostics make it possible to optimize the surgical treatment of complicated forms of chronic pancreatitis and prevent the development of postoperative pancreatic fistula.

Key words: chronic pancreatitis; pancreatic cancer; punch biopsy; complications; surgical treatment.

Among the diseases of the digestive system, chronic pancreatitis (CP) deserves special attention. Although it accounts for only 5–10% of all digestive diseases, it ranks 3rd among them and is considered one of the main risk factors for pancreatic cancer (PC), which accounts for about 10% of all digestive cancers [1, 2]. The risk of developing pancreatic cancer increases by 16 times in the presence of CP [3 – 5]. Other risk factors for developing pancreatic cancer include age over 65 years, smoking, body mass index (BMI) of 25.0–29.9 kg/m^2 , alcohol consumption, and diabetes mellitus (DM).

Pancreatic ductal adenocarcinoma (PDAC) is a type of exocrine cancer with a 95% incidence. The only possible radical treatment for this aggressive malignancy is its surgical removal. However, the vast majority of patients at the time of clinical manifestation of the disease have an advanced state when only palliative surgical correction is possible [6].

The combination of T2DM and CVD as risk factors for the development of PCa can especially increase the progression and malignization of the disease up to ductal adenocarcinoma of the prostate [7]. Thus, long–term diabetes mellitus moderately increases the risk of developing ductal adenocarcinoma of the prostate, but diabetes mellitus that occurs suddenly in adulthood is a marker of possible, already existing, but preclinical ductal adenocarcinoma of the prostate

[8, 9]. In advanced forms of CP with severe pancreatic insufficiency, given the well–known risk of developing PCa, surgeons in the world's leading centers are increasingly inclined to advanced resection interventions, which, in our opinion, is justified in terms of further malignization of the pancreatic tissue and early PCa, as well as prevention of the growth of pancreatic insufficiency [10].

Pancreatic endocrine insufficiency is diagnosed in 45–65% of patients with pancreatic tumors. According to most authors, newly diagnosed diabetes in adulthood is a reliable prognostic sign of existing PCa or its detection in the future. According to T. Muniraj [11], DM is diagnosed simultaneously with PCa in about 50–60% of patients, while the frequency of newly diagnosed hyperglycemia after established PCa reaches 80% [12].

Surgery on the pancreas remains the only radical method of treating pancreatic cancer. Thanks to advances in surgical techniques and perioperative management, early mortality after pancreaticoduodenectomy (PDD) and other resectional interventions in large centers has decreased to 3%. Postoperative pancreatic fistula (POPF) is considered a frequent complication. Previous prospective studies have reported an incidence of PFU of more than 10% and that it is the most common fatal complication after drainage and resectional surgery, regardless of the type of surgery. According to the 2016 International Study Group for Pancreatic Surgery (ISGPS) [13], PAP is defined as a drainage fluid with elevated amylase levels on day 3 after surgery, and the severity of this complication is assessed according to the amount of correction required. Class B (treatment consists only of antibiotics and long–term drainage) and class C (reoperation is required, there is a threat of organ failure leading to death) are defined as clinically significant [13–16]. PAP is mainly caused by leakage of pancreatic juice into the abdominal cavity in case of insufficiency of the pancreatic stump, pancreatic jejunoanastomosis or defect due to necrosis of the pancreatic tissue, which leads to intraperitoneal abscesses, bleeding with a mortality rate of up to 40% and sometimes requires prophylactic total pancreatectomy (stump extirpation) as an alternative to pancreatic jejunostomy [13, 17–19]. The risk factors for the development of PAP include soft consistency of the pancreas, narrow diameter of the main duct, the amount (thickness) of intersecting pancreatic tissue, density (in Hounsfield units) of the parenchyma, and a significant percentage of visceral fat [14]. At the Third World Forum on Pancreatic Diseases in Bern in 2020, the ISGPS consensus classification of PBC risk based on the structure of the prostate ("soft" and "non–soft", e.g., solid, fibrous, or sclerotic) and the size of its main duct (up to 3 mm or more than 3 mm) was approved [20].

The aim of the study was to analyze the results of surgical treatment of patients with pancreatic insufficiency and a high risk of developing PCa.

Materials and methods

The study included 39 patients who were treated in 2019–2023. The average age of patients was 53 years (34–77 years). In 20 (51%) patients assigned to the main group, it was difficult to clearly differentiate between CP and PCa even with a full preoperative examination, even with a full conventional preoperative examination. Quite often, the clinical symptoms and diagnostic picture of these diseases are similar. Therefore, it is difficult to verify an accurate diagnosis immediately before surgery, namely laparotomy and intraoperative rapid diagnosis of the pancreatic parenchyma. In the remaining 19 (49%) patients (conditionally control group), the diagnosis of CP was not in doubt, which was confirmed by changes during diagnostic examinations and the presence of ductal hypertension.

The patients included in the study had a burdened medical history at the beginning of the diagnostic and treatment process, which is inherent in the complicated course of CP. They were repeatedly treated for acute pancreatitis and exacerbation of CP. In 29 (74%) patients, 17 (59%) men and 12 (41%) women, moderate to severe exocrine insufficiency was observed, confirmed by a significant decrease in the level of fecal elastase–1 , which was manifested by digestive disorders, weight loss, and weakness. Sarcopenia was confirmed in 5 (13%) patients who had an extremely advanced condition and a BMI of less than 19 kg/m^2 .

Newly diagnosed in adulthood, DM was diagnosed in 14 (36%) of 39 patients. It is described in the current literature as type 3 diabetes [13, 21]. Taking into account the diagnosis and careful analysis of the results, it was confirmed that 75% of patients in this group had endocrine and exocrine insufficiency, which is characteristic of decompensated, fibrotic pancreas and is defined as pancreatic insufficiency [8, 9, 22].

All patients with complicated forms of CP and suspected pancreatic tumor underwent a set of laboratory tests, which included a complete blood count (determination of hemoglobin concentration, leukocyte count, erythrocyte sedimentation rate, hematocrit, and leukocyte formula calculation). Serum biochemical parameters included total protein, total bilirubin and its distribution by fractions, urea, creatinine, liver enzyme activity, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glucose, sodium, potassium, serum calcium, and C–peptide. The tumor marker CA 19–9 (Carbohydrate Antigen 19–9), a cancer–embryonic antigen, was also studied. Fecal elastase–1 levels were determined to confirm the presence of pancreatic exocrine insufficiency, which develops in both CP, cystic fibrosis, and pancreatic tumors or diabetes. In patients undergoing examination and treatment in the hospital, routine screening methods of instrumental diagnostics were used – fibroesophagogastroduodenoscopy, ultrasound (US), computed tomography of the abdominal cavity.

In addition to standard methods of examination, the levels of matrix metalloproteinases (MMPs) 1, 2, 3, 8, 9, 10 and tissue inhibitor of metalloproteinases (TIMP) in blood plasma were studied, which are considered to be modern biomarkers for the diagnosis of PCa. At the preclinical – early stage, the levels of TIMP–1, MMP–9, urokinase plasminogen activator and its receptor, cytokinin macrophage inhibitor were determined by mass spectrometry [2, 23].

According to the decision of the Bioethics Commission of Vinnytsia National Medical University named after M. Pirogov (Minutes of the Commission's meeting No. 15 of September 26, 2021), the studies fully complied with the ethical and moral requirements of the current provisions of the orders of the Ministry of Health of Ukraine and the Declaration of Helsinki of the World Medical Association for the Principles for Scientific Medical Research Involving Human Subjects. We obtained the consent of the patients who were treated for all studies, as well as for the collection, study and analysis of excess material.

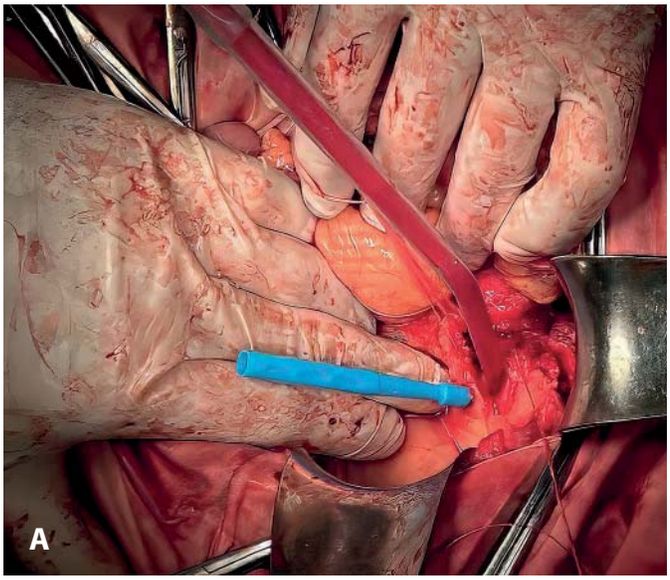
Results

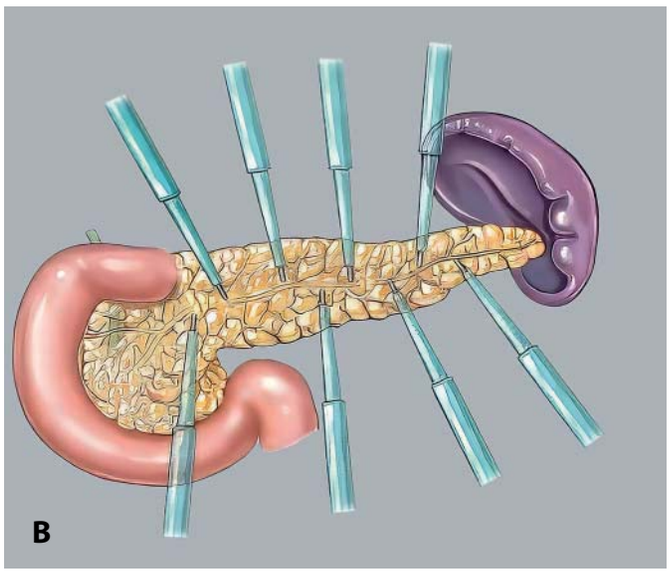
The changes we obtained were directly correlated with the results of the previous experimental study. We have published the direct detailed results previously [24, 25].

Our data on the increase in MMP levels in the prostate tissue of patients with CP and patients with PCa are similar to the results published by other authors, which indicate an active role of these enzymes in remodeling the extracellular matrix, which in the presence of chronic inflammation of the prostate promotes fibrosis, and in the presence of PCa facilitates invasion, angiogenesis, and metastasis.

Consideration of changes in the protein profile of blood plasma and pancreatic tissue, total proteolytic activity, MMP and serine proteinases in the pancreas during the experimental part of the work, as well as the study of changes in the blood plasma of patients at risk in the preoperative period, became the basis for focusing on intraoperative multiple biopsy as an obligatory component of surgical care for a clear differential diagnosis of CP and possible PCa.

A classic biopsy is performed in the most convenient place for the doctor and the safest place for the patient to prevent the development of possible complications. In case of a conditionally negative result, it is possible to perform a drainage operation and form an anastomosis on the already malignantly degenerated prostate tissue. Therefore, we have improved this method. In the presence of complicated PD





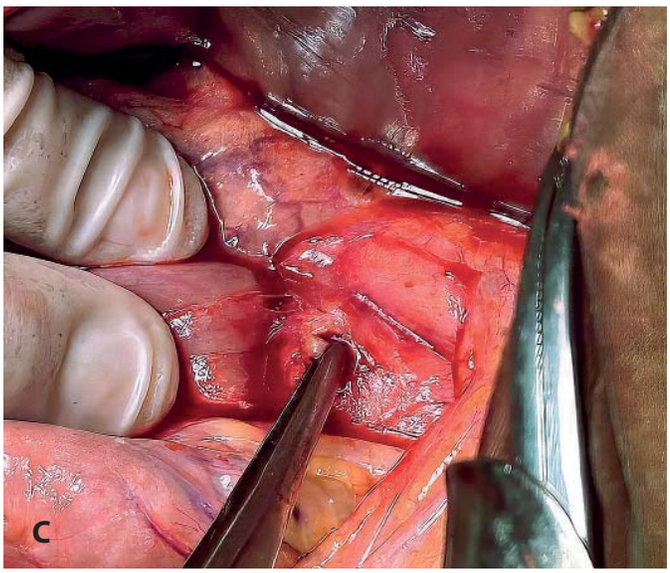


Figure 1.
Multiple punch biopsy of the software:
A - intraoperative removal of the prostate; B - scheme of puncture biopsy, C - excision of the biopsy column from the surgical field with subsequent rapid diagnosis.

during surgery, the biopsy was taken using a special punch device, the appearance of which resembles a pen, along the entire length of the main duct of the prostate along the upper and lower edges of the dissection in a checkerboard pattern (Fig. 1). Material sampling is safe and complete with rapid examination and the most effective surgical intervention (Fig. 2).

There were no complications of punch biopsy. The study included patients with fibrotic tissue, so it was safe to obtain a biopsy with a diameter of 2 mm, and the development of postoperative pancreatitis was not established.

Among the 20 (51%) operated patients in the main group, 12 (60%) were diagnosed with diabetes mellitus with characteristic changes in MMP and peptide pool, which is typical of malignant tissue. Intraoperatively, after performing a punch biopsy, acinar metaplasia was diagnosed in 3 (25%) patients, in 5 (42%) patients – changes in the pancreatic tissue characteristic of pancreatic intraductal neoplasia (PanIN) of a high level according to the Baltimore Consensus of 2014, in 4 (33%) patients, the presence of PCa with localization in the head was confirmed intraoperatively. Changes in the plasma protein profile identified at the preoperative stage, as well as characteristic changes in the prostate tissue, justified the performance of extended resection interventions in these patients: Whipple surgery in 7 (58%) and left–sided distal resection in 5 (42%).

In the remaining 8 (40%) patients with complicated CP, ductal hypertension, pain syndrome, but without morphological changes inherent in malignancy, we performed Whipple surgery – in 2 (25%) patients with severe fibrous changes in the head of the pancreas and significant pain syndrome; drainage surgery, namely longitudinal pancreaticoduodenostomy – in 2 (25%) patients with ductal hypertension and pain syndrome, Frey's surgery with frontal resection of the pan-

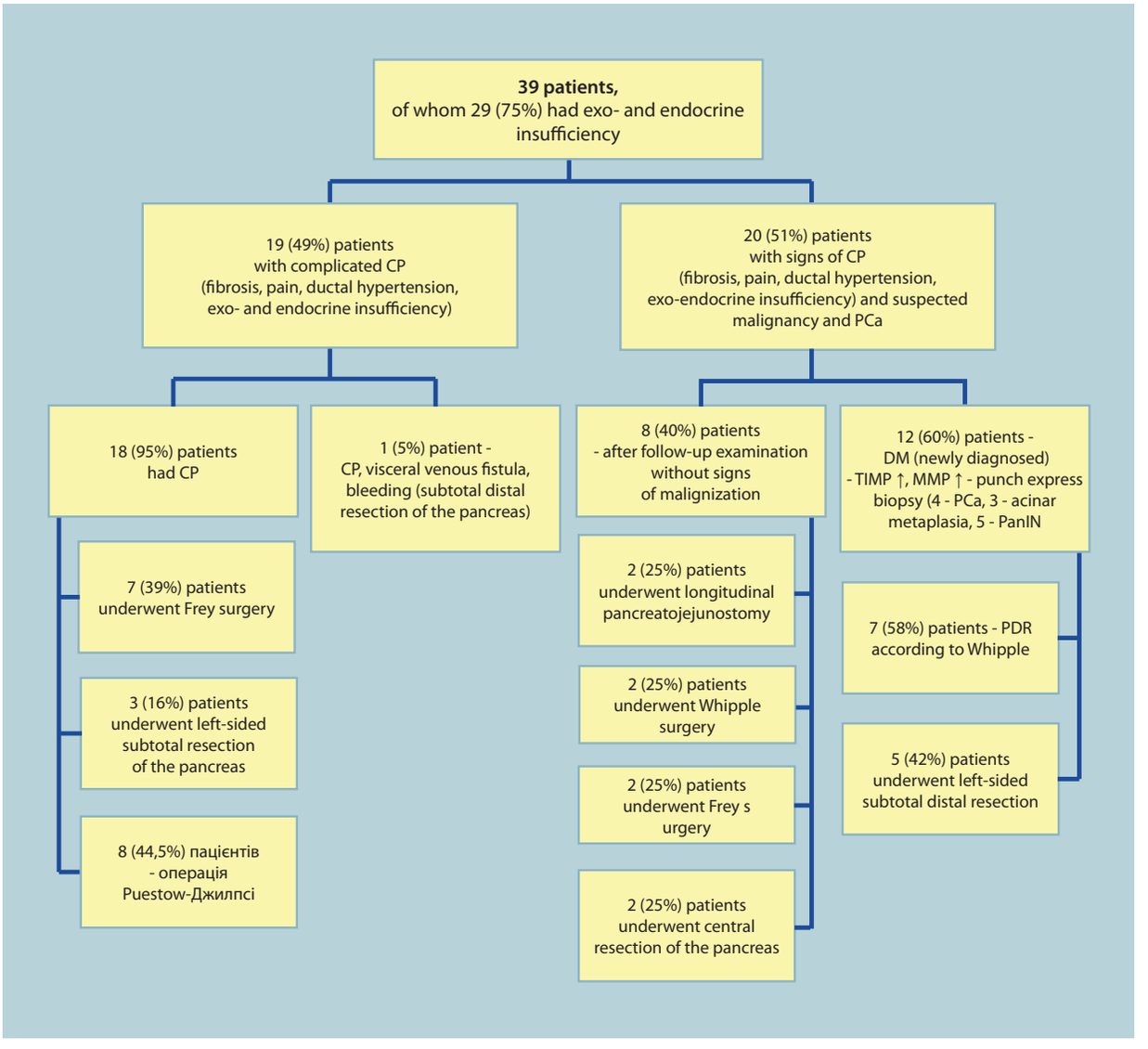


Fig. 2.
Algorithm of surgical treatment of CP with a high risk of developing PCa.

creas – in 2 (25%) patients; our proposed central resection of the prostate with preservation of the left anatomical segment (copyright certificate No. 120597 dated 18.07.2023) to prevent the growth of further pancreatic insufficiency (Fig. 3) – in 2 (25%) patients.

All 19 (49%) patients of the conditional control group with complicated forms of CP underwent appropriate drainage and resectional surgical interventions: Frey's operation – 7 (37%), Puestow–Jilpsey operation – 8 (42%), left–sided subtotal resection – 3 (16%), subtotal distal resection, which was caused by an existing virsungo–venous fistula diagnosed during surgery and confirmed by intraoperative virsungography – 1 (5%). In our opinion, the fistula was caused by a false splenic vein aneurysm with frequent gastrointestinal bleeding through the main duct of the pancreas and, as a result, through the large duodenal papilla.

Complications occurred in 2 patients after radical surgical interventions for PCa localized in the head. In the early postoperative period, 1 patient after Whipple surgery, despite all the measures taken, developed gastrostasis with a flow rate of about 2 – 2.5 liters per day. On the 11th day, a relaparotomy with reconstruction of the gastroenteroanastomosis was performed. Another patient was diagnosed with a subhepatic abscess (biloma) on the 30th day, which was clinically manifested by hyperemia and weakness. Drainage through a subcostal mini–access had a positive effect.

In 2 patients, after left–sided resection of the prostate, subdiaphragmatic abscesses were diagnosed on the left side, which formed despite the prolonged leaving of drains. They were treated minimally invasively by puncture and drainage under ultrasound guidance. In one patient, the abscess was a result of partial failure of the prostate stump, and in another patient with PCa, a lymphocele (Chyle leak) with infection formed after extended left–sided subtotal resection of the prostate with splenectomy due to lymphoma.

Multiple organ failure occurred in 1 patient after surgery for internal pancreatic fistula, infected ascites as a complication of neglected CP. The patient was emaciated (BMI 16 kg/m^2), had severe ascites and severe comorbidities. He died. Infection of the midline laparotomy wound occurred in 4 patients, but it was diagnosed at an early stage and healing was achieved by controlled primary tension.

Class B PAPF occurred in 3 (7.7%) patients after left–sided resection of the pancreas (2) and after longitudinal pancreaticoduodenostomy (1). In 1 patient, a class C fistula was formed after a combined (resection and drainage) intervention. Relaparotomy, subtotal resection with Ruh loop closure were performed.

Discussion

According to the most recent Global Cancer Statistics 2022, PCa is characterized as a disease that has a poor response to treatment and a poor prognosis. Over the past three decades, the global annual number of patients with PCa has increased by more than 2.5 times. In 2020 and 2017, approximately 495,773 and 441,000 newly diagnosed patients with PCa were registered worldwide, respectively, compared to 196,000 in 1990. According to the latest data, 510,992 patients with PCa were registered in 2022, of whom 467,409 died. Worldwide, PCa has been identified as the leading cause of cancer–related deaths [13]. Therefore, given the social aspects, relatively low 5–year survival rate of patients, the study of this problem is becoming more relevant every year [26–29].

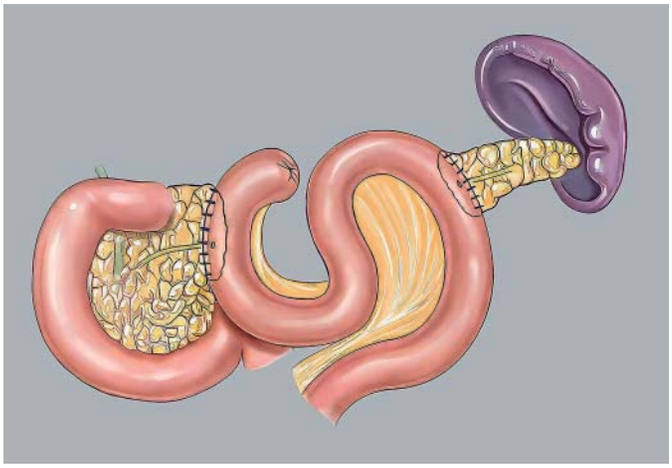


Fig. 3.
Modified pancreaticojejunal anastomoses.

A review of recent studies on CP and the development of PCa demonstrates the depth of the problem and confirms the imperfect understanding of the progression of the process up to the development of malignancy. Differential diagnosis of these two diseases is difficult. Undiagnosed PCa, which is perceived as a disease of the same type and treated appropriately, is associated with high mortality due to the delay in adequate treatment. There is a need for further research on radiomics, metabolomics, peptide pools, multiple biopsies to increase the sensitivity and specificity of both imaging methods and biomarkers used today, so that it is possible to differentiate between CP and PCa as quickly and accurately as possible [30].

Patients included in the study had severe fibrotic changes in the pancreatic tissue provoked by activation of pancreatic stellate cells in the early stages of the disease. Patients with ductal hypertension, which develops with the progression of CP, complained of severe pain. According to the latest International Consensus Guidelines for Surgical Treatment and Timing of Intervention in Complicated PD for 2020 [10], drainage or combined (drainage + resection) surgical intervention is indicated to eliminate ductal hypertension, as well as to remove altered parenchyma as a pain maker and in case of suspected malignancy. In our opinion, early sur-

gical interventions, such as Puestow–Gilpsey, Frey, Beger, left–sided distal resection of the pancreas, can achieve the maximum effect. These surgeries have long been known and effective as methods of palliative and symptomatic care for patients with CP and ductal hypertension. For patients with an enlarged head of the pancreas and existing paraduodenal pancreatitis, the Whipple operation is indicated [31–33].

Thus, thanks to a thorough morphological examination, the use of as many diagnostic methods as possible to differentiate between CP and PCa, it is possible to perform the correct and most effective surgical intervention with a decrease in the incidence of postoperative complications, and, if they occur, to deal with them more effectively and radically.

Conclusions

1. Morphologic changes in the prostate tissue in CP in combination with DM, corresponding to the development of PanIN, are direct predictors of prostate adenocarcinoma. Multiple intraoperative biopsy of the prostate is effective for verification of malignant prostate tissue, as well as a high risk of developing PCa in complicated forms of CP with clinical manifestation.

2. Determination of changes in the characteristics of the peptide pool in the blood plasma of patients in the preoperative period allows to make a decision on the adequate volume of surgical intervention and, accordingly, to prevent the development of early postoperative complications and avoid relaparotomy.

3. The use of pre– and intraoperative diagnostic methods makes it possible to optimize surgical treatment in complicated forms of CP, as well as to predict and prevent complications in the form of PON by increasing the resection volume up to subtotal resection.

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Authors' contributions. All authors contributed equally to this work.

Conflict of interest. The authors who participated in this study have declared that they have no conflicts of interest regarding this manuscript.

Consent for publication. All authors have read and approved the final version of the manuscript. All authors have agreed to the publication of this manuscript.

Ethical considerations. All procedures performed in the study with the involvement of patients complied with ethical standards for clinical practice and the Declaration of Helsinki, 1964, as amended.

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