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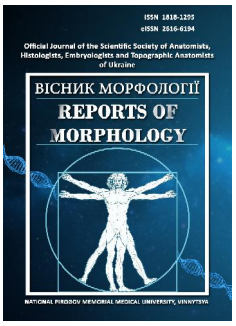


# Optimization of the selection of the volume of surgical intervention in cases of pronounced morphological and structural changes of the parenchyma in patients with a high risk of developing pancreatic cancer

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*Chronic pancreatitis is a common recurrent pathology of the pancreas. The long course of the inflammatory process, accompanied by chronicity, is often attributed to the causes that lead to the development of pancreatic cancer. The aim of the work is to study the morphological changes of the pancreas in rats and the level of of matrix metalloproteinases and tissue inhibitor of metalloproteinases in patients with complicated forms of chronic pancreatitis and a high risk of developing pancreatic cancer in order to optimize the selection of the volume of surgical intervention. A histological study of the pancreas of rats with chronic pancreatitis and chronic pancreatitis on the background of diabetes was carried out. 27 patients operated on during 2020-2022 were examined. In 15 of them, we were unable to clearly and convincingly differentiate of chronic pancreatitis from pancreatic cancer, since quite often the clinical symptoms and diagnostic picture of these diseases are similar. In the remaining 12 patients it was confirmed with all the inherent clinical signs of chronic pancreatitis and ductal hypertension. Matrix metalloproteinases (MMP-1, -2, -3, -8, -9, -10) and tissue inhibitor of metalloproteinases were studied. The obtained results were processed statistically. Morphological changes of the pancreas in rats correspond to high and moderate ductal dysplasia of the PanIN 2 and PanIN 3 class, which are direct predictors of pancreatic adenocarcinoma. In 22 patients moderate and severe exocrine insufficiency was observed, confirmed by a significant decrease in fecal elastase. An intraoperative biopsy of the changed tissue of the pancreas was performed. Among the 15 operated patients of the main group, 9 were diagnosed with diabetes mellitus and changes in MMTs and a peptide pool inherent in malignant tissue. Intraoperatively, after performing a punch biopsy, acinar metaplasia was detected in 3 patients, tissue changes characteristic of PanIN2-PanIN3 in 4 patients, and pancreatic cancer in the head area was confirmed in 3 patients. Changes in the protein profile of the plasma, clinical manifestations, as well as characteristic changes in the pancreas tissue, gave us grounds for performing extended resection interventions. Studying the morphological structure of the pancreas, using as many methods as possible for differential diagnosis between chronic pancreatitis and pancreatic cancer, as well as a comprehensive approach to the patient will allow for the most correct and effective intervention.*

**Keywords:** *pancreas, morphological changes, chronic pancreatitis, fibrosis, pancreatic ductal adenocarcinoma.*

## Introduction

Chronic pancreatitis is a common recurrent pathology of the pancreas. The long course of the inflammatory process, accompanied by chronicity, is often attributed to the causes that lead to the development of a pathology with

an extremely unfavorable prognosis - pancreatic cancer. That is why the search for diagnostic criteria that would allow predicting the transition of inflammatory processes in the tissue of the pancreas to hyperproliferative processes and the risk of developing pancreatic cancer is gaining relevance [13].

According to the study results, in pancreatic injury due to KRAS hyperactivity and increased inflammatory signaling with loss of cell-cell and cell-matrix contacts, loss of polarity can induce acinar cells to transdifferentiate to a duct-like phenotype with acinar-ductal metaplasia and initiate further progression to low-grade degree of precancerous lesions [1, 10, 30]. Chronic stimulation and proliferation of the pancreatic duct in response to islets of Langerhans inflammation in type 2 diabetes is associated with an increased risk of pancreatic cancer with concomitant type 2 diabetes [9, 14]. Ductal adenocarcinoma of the pancreas is a type of exocrine cancer and accounts for 95 % of all pancreatic cancers. It is an aggressive malignant tumor, and surgical removal of the tumor is the only possible radical treatment. However, up to 90 % of patients, at the time of clinical manifestation of the disease, have a neglected condition and are surgically incurable [2]. TNF-α expression is increased during the initiation of pancreatic ductal adenocarcinoma, and anti-TNF-α antibodies have shown promising effects in ductal adenocarcinoma in preclinical models by killing tumor cells and reducing desmoplasia and inflammation in the tumor stroma of pancreatic ductal adenocarcinoma [28].

Pancreatic stellate cells (PSCs) can synthesize and secrete acetylcholine and play a role in mediating exocrine secretion from acinar cells. PSCs transform into activated myofibroblast-like cells in response to inflammation. These cells play an important role in the progression of chronic pancreatitis to pancreatic cancer. PSCs respond to proinflammatory cytokines in acute pancreatitis and may progress to chronic pancreatitis with pancreatic damage, fibrosis, diabetes, and metaplasia [22, 31].

Because both diabetes mellitus and chronic pancreatitis are risk factors for pancreatic ductal adenocarcinoma, their combination may particularly raise concerns about progression and malignancy to pancreatic ductal adenocarcinoma. [26]. In a population-based cohort study in Taiwan, the risk of malignancy and development of pancreatic ductal adenocarcinoma was significantly increased in participants with existing diabetes and chronic pancreatitis (hazard ratio 33.5) [19]. Separate research databases also showed an increased, but slightly more modest, hazard ratio (4.7-12.1) for pancreatic ductal adenocarcinoma in individuals with unclassified diabetes and a history of chronic pancreatitis [21].

In other studies, subgroups of participants with newly diagnosed diabetes showed an even higher prevalence of pancreatic ductal adenocarcinoma (5.2-13.6 %). Thus, while long-standing diabetes moderately increases the risk of pancreatic ductal adenocarcinoma, adult-onset diabetes is a marker of possible pre-existing, but preclinical, pancreatic ductal adenocarcinoma. [11, 24].

*The aim of the work* is to study the morphological changes of the pancreas in rats and the level of of matrix metalloproteinases and tissue inhibitor of metalloproteinases in patients with complicated forms of chronic pancreatitis and a high risk of developing pancreatic cancer in order to optimize the selection of the volume of surgical intervention.

## Materials and methods

The study included 27 patients, the average age of which was 56 years (39-77 years). In 15 of them (55 %), despite a thorough preoperative examination, it was impossible to clearly and convincingly differentiate chronic pancreatitis from pancreatic cancer, because the clinical symptoms and diagnostic picture of these diseases are similar. In the remaining 12 (45 %) patients, the diagnosis of chronic pancreatitis was confirmed by all inherent clinical signs and existing ductal hypertension.

The patients who were included in the study cohort had a complicated medical history at the time of the beginning of the diagnostic and treatment process. They were repeatedly treated for acute and exacerbation of chronic pancreatitis after dieting, as well as alcohol abuse and smoking. In 22 (83 %) patients (13 men - 60 %, 9 women - 40 %) moderate and severe exocrine insufficiency was observed, confirmed by a significant decrease in fecal elastase, manifested by indigestion, weight loss, and weakness. In some cases, we observed sarcopenia, which did not allow patients to live without external assistance.

First-onset diabetes in adulthood was diagnosed in 9 (33.5 %) of 27 patients. In medical literature, it is interpreted as type 3 diabetes. This means, the majority of the group has endo- and exocrine insufficiency, which is a characteristic of a decompensated, fibrotic pancreas. According to the results of research by various authors [4, 11, 24], diabetes that occurs suddenly in adulthood in patients with pancreatic pathology is one of the predictors of the development of cancer of this organ.

According to the decision of the bioethical commission of the National Pirogov Memorial Medical University, Vinnytsia, Ukraine (protocol No. 15 dated 26.09.2021), the conducted research fully met the ethical and moral and legal requirements of the current provisions of the Ministry of Health of Ukraine and the Helsinki Declaration of the World Medical Association on the principles of conducting scientific medical research with human participation.

We conducted studies of matrix metalloproteinases (MMP-1, -2, -3, -8, -9, -10) and tissue inhibitor of metalloproteinases (TIMP) in the plasma of patients and obtained changes that directly correlate with the results of our experimental study, which we presented in our previous works.

An experimental study was conducted, in which 50 non-linear white adult male rats weighing 200.0±10.0 g were used. When working with laboratory animals, international recommendations on conducting medical and biological

research using animals were followed in accordance with the "General principles of work on animals", approved by the 1st National Congress on Bioethics (Kyiv, Ukraine, 2001) and agreed with the provisions of the "European Convention for the Protection of Vertebrates" animals used for experimental and other scientific purposes" (Strasbourg, France, 1986). Experimental work with rats was carried out in the vivarium of Taras Shevchenko Kyiv National University. Work with animals was regulated by the rules for conducting experimental work with experimental animals, which were approved by the bioethical commission of Educational and Scientific Centre "Institute of Biology and Medicine" at Taras Shevchenko National University of Kyiv.

Chronic pancreatitis was induced by intraperitoneal injection of cerulein (Sigma, St. Louis, MO, USA) diluted in saline (5.0 μg/kg) five times a day at one-hour intervals. Control rats received equal volumes of 0.9 % NaCl administered intraperitoneally. Injections were carried out for five consecutive days. After the last day of cerulein injection, the rats were kept under standard conditions, without restriction in access to water, for the next 9 days. The development of pancreatitis was confirmed by a high level of amylase in blood serum, as well as by the study of pathogistological changes in the pancreas` parenchyma of the rats under experiment. On the 14th day from the beginning of the experiment, half of the animals from the chronic pancreatitis group were randomly selected and diabetes was induced in them. Diabetes mellitus was induced in rats after a 16-hour fast with a single intraperitoneal injection of streptozotocin (STZ; Sigma, USA) at a dose (65.0 mg/kg) dissolved in 0.5 ml of freshly prepared 0.01 M citrate buffer (pH 4.5). Other animals from the chronic pancreatitis group and all control rats received an equal volume of placebo. The diagnosis of diabetes was confirmed on the basis of a high blood glucose concentration (above 15 mmol/l). Animals were removed from the experiment on the 134th day after the beginning of cerulein administration.

Statistical processing of the obtained results was carried out using the methods of variational statistics using the computer program Excel (Microsoft corporation, USA).

## Results

Histological examination of the changed tissue of the pancreas of experimental groups of animals established pathological changes in the group of chronic pancreatitis (Fig. 1) and chronic pancreatitis+diabetes (Fig. 2). In the group of chronic pancreatitis, changes in the pancreas are characterized by the presence of fibrosis in all animals of this group. In most cases, growth of fibrous tissue with polymorphic cellular inflammatory infiltration was observed. In half of the animals with experimental chronic pancreatitis, the interlobular excretory duct wall fibrosis with the formation of glands in the fibrous tissue of the duct was detected. Proliferation of the glandular epithelium with dysplasia also developed. The changes described are classified as PanIN 1.

The pancreas of rats in the chronic pancreatitis + diabetes group had more pronounced changes (Fig. 3). Adherence to ductal dysplasia (see Fig. 3, Fig. 4) was also observed with pronounced acinar metaplasia (Fig. 5). The formation of glands in the fibrous tissue of the duct, the proliferation of glandular epithelium with pronounced dysplasia, the appearance of papillary and cribriform structures corresponding to high and moderate ductal dysplasia of the PanIN 2 and PanIN 3 class - these changes are direct predictors of pancreatic adenocarcinoma. The development of PanIN is a route to pancreatic cancer and directly to ductal adenocarcinoma.

Significant differences in the content of individual forms of MMP in the blood plasma and in the pancreatic tissue of patients with chronic pancreatitis compared to the control group were established. The greatest changes were found in the pathologically changed tissue of the pancreas. The

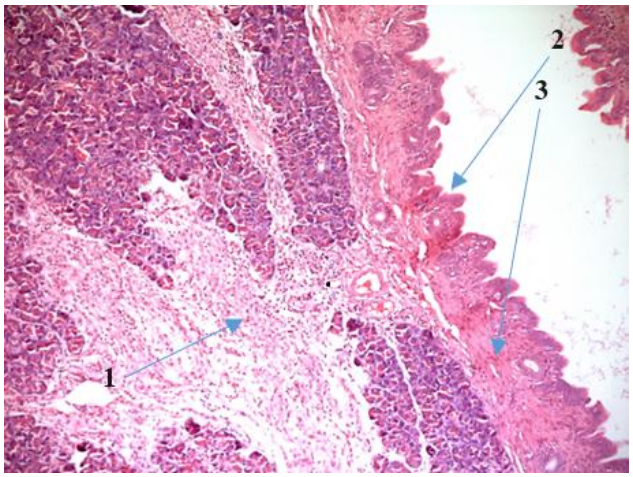


**Fig. 1.** Morphological changes of pancreatic tissue in conditions of chronic pancreatitis. Growth of fibrous tissue (1) with polymorphic cellular inflammatory infiltration (2, 3). Hematoxylin-eosin staining, x100.

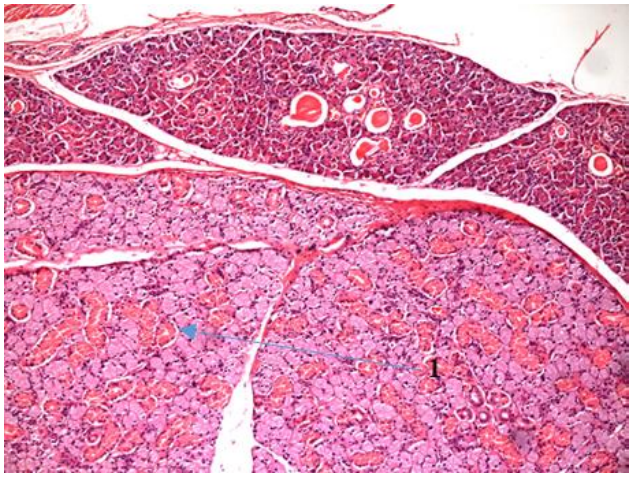


**Fig. 2.** Morphological changes of pancreatic tissue in conditions of chronic pancreatitis in combination with diabetes. Fibrous tissue growth (1) associated with ductal dysplasia. Hematoxylin-eosin staining, x100.

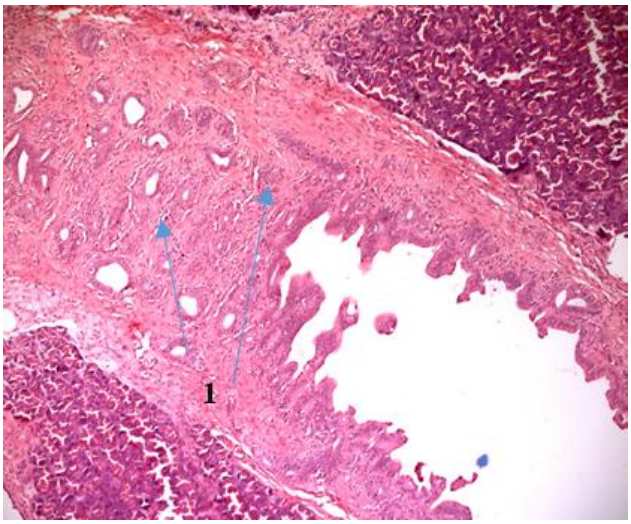


**Fig. 3.** Morphological changes of pancreatic tissue in conditions of chronic pancreatitis in combination with diabetes. The formation of glands in the fibrous tissue of the duct, the proliferation of the epithelium with its dysplasia and the formation of papillary structures. PanIN 2-3 (1). Staining with hematoxylin-eosin x100.

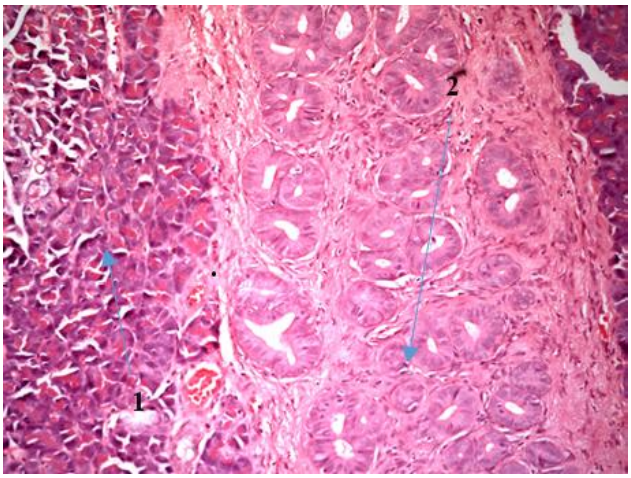


**Fig. 4.** Morphological changes of pancreatic tissue in conditions of chronic pancreatitis in combination with diabetes. Proliferation of glandular epithelium with severe dysplasia (1), formation of papillary (2), cribrose structures. PanIN 3. Hematoxylin-eosin staining, x400.

increase in the concentration of MMP in the blood plasma of patients with chronic pancreatitis was maximal for the collagenases MMP-1 and MMP-8 and amounted to 80 %, $p<0.05$, further decreasing in the following series: MMP-2 (50 %, $p<0.05$), MMP-3 (42 %, $p<0.05$), MMP-10 (40 %, $p<0.05$). A compensatory increase in the content of TIMP in the systemic circulation was established under conditions of chronic pancreatitis (by 67 %, $p<0.05$). In contrast to chronic pancreatitis, in the presence of pancreatic cancer, the plasma levels of all studied parameters did not reliably differ from those of the control group, probably due to the local involvement of the studied enzymes in the processes of tumorigenesis - precisely at the tissue level, in the place of their secretion, and not in the systemic circulation

These assumptions are consistent with the results obtained by us, when studying the content of MMP and TIMP in pancreatic tissue, according to which the levels of all investigated indicators of patients with both chronic pancreatitis and pancreatic cancer were significantly higher than those in the control group. In chronic pancreatitis, the maximum increase in content was also found for MMP-1 collagenase (3.2 times, $p<0.05$); the levels of other MMPs increased as follows (MMP-8 - by 2.7 times, $p<0.05$; MMP-9 and MMP-10 - by 2.3 times, $p<0.05$; MMP-3 - by 83 %, $p<0.05$; MMP-2 - by 66 % $p<0.05$), and the content of TIMP increased 2.6 times ($p<0.05$). The content of MMP in pancreatic tissue under cancer conditions exceeded the corresponding levels of the control group: gelatinase MMP-9 - 3.3 times ($p<0.05$), stromelysin MMP-10 - 3.1 times ($p<0.05$) and collagenase MMP-8 and MMP-1 - 2.9 times ($p<0.05$), MMP-3 - 2.7 times ($p<0.05$) and MMP-2 - 2.3 times ($p<0.05$). The content of TIMR exceeded the similar indicator of the control group by 3.1 times. At the same time, the levels of MMP-2, -3, -9, -10 and TIMP in the pancreatic tissue of patients with pancreatic cancer were higher than the levels of the corresponding indicators for the group of patients with chronic pancreatitis - by 39 %, 48 %, 43 %, 34 %, 19 %, respectively, $p<0.05$.

The data we obtained regarding the increase in the levels of MMP in the pancreatic tissue of patients with chronic pancreatitis and pancreatic cancer is consistent with the currently available literature data, which indicate the active role of these enzymes in the remodeling of the extracellular matrix, which in the case of chronic pancreatitis contributes to the development of pancreatic fibrosis. and in the presence of pancreatic cancer, it facilitates invasion, angiogenesis and metastasis.

Taking into account the changes in the protein profile of the plasma and pancreatic tissue, total proteolytic activity,

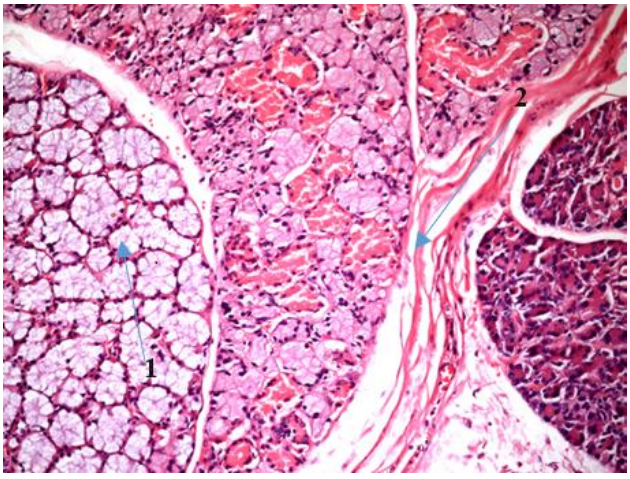


**Fig. 5.** Morphological changes of pancreatic tissue in conditions of chronic pancreatitis in combination with diabetes. Pronounced acinar metaplasia (1). The appearance of papillary and cribriform structures corresponding to high and moderate ductal dysplasia of the PanIN 2 and PanIN 3 class (2). Hematoxylin-eosin staining. x400.

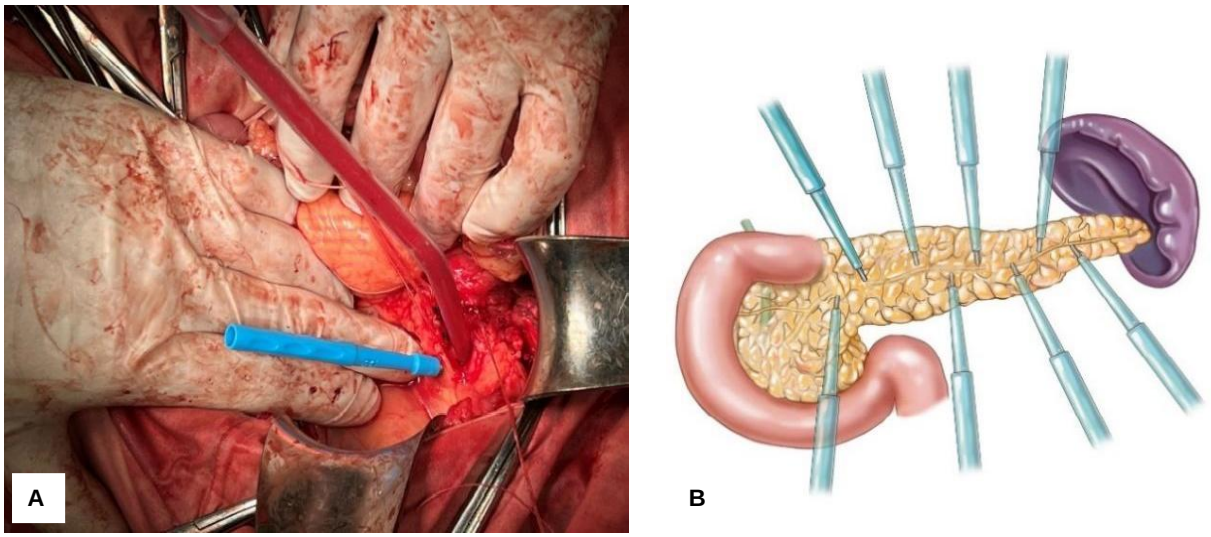


**Fig. 6.** Multiple punch biopsy of the pancreas. A - intraoperative removal of the pancreas, B - scheme of puncture biopsy.

MMP and serine proteinase activity in the pancreas in the experiment, as well as studying the changes in the blood plasma in the preoperative period of patients at risk, we focused on intraoperative biopsy and diagnosis.

Usually, the surgeon performs the biopsy in the most convenient place for the doctor and the safest place for the patient to ensure the prevention of possible complications (bleeding, acute postoperative pancreatitis, pancreatic fistula). Therefore, from the diagnostic point of view of, the effectiveness of this biopsy and its result are often questionable and ineffective. The possibility of performing a draining operation and forming an anastomosis on already malignantly regenerated tissue is not excluded. Therefore, we improved this method, and the uniqueness and novelty were confirmed by obtaining a certificate of copyright registration. In the case of complicated chronic pancreatitis during surgery, a biopsy is taken with a punch pen along the entire length of the Wirsung duct along its upper and lower edges of the dissection in a chequerwise manner along the entire length of the gland. Thus, during the study, a safe and complete collection of material takes place (Fig. 6).

In the same patients, we implemented scraping from the duct in the proximal and distal directions, which is effective, considering that 95 % of malignant tumors of the pancreas are ductal adenocarcinoma (Figs. 7, 8).

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

Among 15 (55 %) operated patients of the main group, 9 (60 %) were diagnosed with diabetes with changes in MMP and peptide pool, which was characteristic of malignant tissue. Intraoperatively, after performing a punch biopsy, 3 (33 %) were diagnosed with acinar metaplasia, 4 (44 %) had tissue changes characteristic of PanIN 2-PanIN 3, and 2 (23 %) were intraoperatively confirmed to have pancreatic cancer localized in its head. Changes in the protein profile of the plasma, which we determined at the preoperative stage, as well as characteristic changes in the tissue of the pancreas, provided the basis for performing extended resection interventions. Therefore, 5 (30 %)

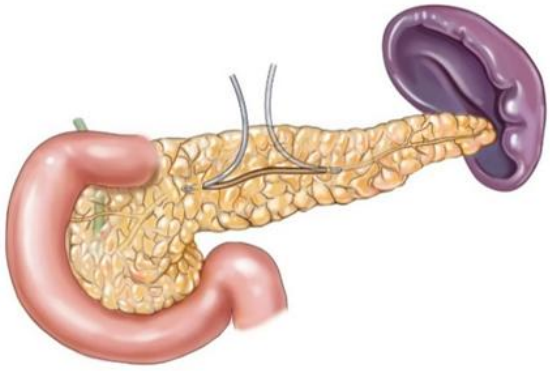

**Fig. 7.** Schematic representation of the scraping site of the altered pancreatic duct.

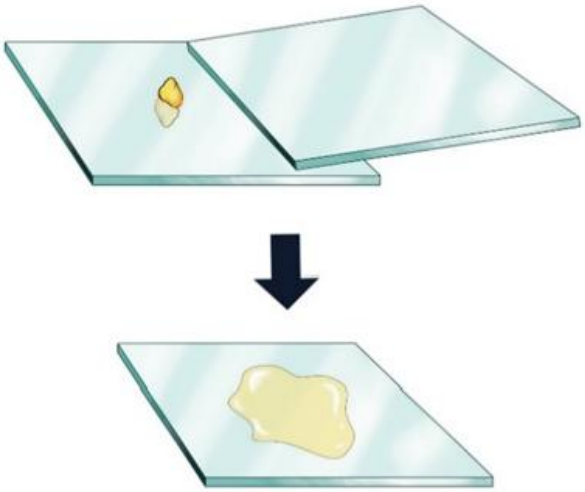

**Fig. 8.** Cytological express study.

Whipple operations and 6 (40 %) left-sided distal resections were performed. In the remaining four (30 %) patients with complicated chronic pancreatitis, ductal hypertension, pain syndrome, but without suspicion of malignancy, drainage surgery was performed.

## Discussion

According to the latest and most up-to-date data from Global Cancer Statistics 2020, pancreatic cancer is a fatal disease characterized by a poor response to treatment and a poor prognosis. A more than 2.5-fold increase in the global annual number of cases has been reported over the past three decades. There were approximately 495,773 and 441,000 newly identified cases of pancreatic cancer worldwide in 2020 and 2017, respectively, compared with 196,000 subjects in 1990. Worldwide, pancreatic cancer has been identified as the leading cause of cancer-related deaths [3, 17, 29]. Therefore, taking into account the social aspects, the relatively low 5-year survival of patients, the study of this problem becomes more relevant every year [7, 20, 25, 27].

In our studies, we obtained similar results to Gao L. with co-authors [8] and Hart P. A. with co-authors [9] confirming the dependence and relationship between chronic pancreatitis and diabetes in an experiment, which where is manifested by more active inflammation and contributes to tumor development.

In a meta-analysis, Ben Q. and co-authors [4] reported a relative risk of pancreatic cancer of 5.4 (95 % CI 3.5-8.3), which is associated with a duration of diabetes of less than 1 year and a moderate risk of its occurrence in about 1.5 times after 5 years of its course. A population-based study conducted in Rochester, Minnesota, USA, found that approximately 1 % of participants with new-onset diabetes aged 50 years or older had diabetes secondary to pancreatic cancer. It is early and comprehensive diagnosis, according to Caban M. and Malecka-Wojciesko E., as well as screening of the disease in the general population and directly in high-risk groups with the use of various biomarkers of pancreatic cancer, that will allow to diagnose the pathology before the appearance of distant metastases and apply radical surgical intervention [5].

Y. Miyashita and co-authors in a long-term cohort study in Japan state that the metabolic syndrome is closely related to the incidence of pancreatic cancer. In 2005, they recruited approximately 4.6 million Japanese subjects and followed these subjects for over 10 years. Metabolic syndrome has been confirmed to be associated with pancreatic cancer. They also demonstrated an association between pre-metabolic syndrome and pancreatic cancer [23].

Patients with chronic fibrotic changes of the pancreas in the background or in combination with diabetes have a significantly higher risk of malignancy of the process and the development of accompanying complications inherent in this disease. The main focus of our research was to concentrate on the intraoperative diagnosis of complicated chronic pancreatitis and to confirm or deny the development of pancreatic cancer. To do this, we performed an intraoperative multiple poly-punch biopsy and scraping of the Wirsung duct with express (intraoperative) diagnosis and determination of further tactics of surgical intervention. We received a certificate of copyright registration for these methods: "Methodology of intraoperative biopsy of the pancreas" No. 115178 and "Methodology of intraoperative multiple biopsies of the pancreas" No. 114856, respectively. The methods are simple, affordable and were the reason for the change in the surgical correction of pancreatic pathology in the direction of increasing the resection volume, which ensured and guaranteed receiving a more radical treatment.

The patients included in the study had pronounced fibrotic changes in the tissue, which were provoked by the activation of pancreatic stellate cells in the early stages of the disease. Pronounced pain syndrome was characteristic of patients with ductal hypertension, which develops under conditions of progression of chronic pancreatitis. According to the latest International consensus recommendations on surgical treatment and timing of intervention in complicated chronic pancreatitis [15] for 2020, there is drainage or combined (drainage + resection) surgery to eliminate ductal hypertension, as well as altered parenchyma, which is the pacemaker of pain, and in suspicion of malignancy of the process. In order to achieve the maximum effect, today we lean towards early surgical interventions. Such operations include Puestow-Gillesby procedure, Frey procedure, Beger procedure, left-distal resection of the pancreas. These operations have long been known and are effective as palliative and symptomatic care for patients with chronic pancreatitis and ductal hypertension. Whipple surgery is indicated for patients with an enlarged head of the pancreas and existing Groove pancreatitis [6, 12, 16, 18].

Thus, thanks to a careful morphological study, the application of as many methods of differential diagnosis between chronic pancreatitis and pancreatic cancer as possible, it is possible to perform the most correct and effective surgical intervention.

## Conclusion

1. It has been confirmed that the morphological changes of the pancreatic tissue in rats with chronic pancreatitis in combination with diabetes, corresponding to the development of PanIN, are direct predictors of pancreatic adenocarcinoma. The effectiveness of multiple intraoperative biopsies of the pancreas for the verification of malignant tissue of the pancreas, as well as the high risk of developing pancreatic cancer in complicated and clinically manifest forms of chronic pancreatitis, has been proven.

2. The effectiveness of multiple intraoperative biopsies of the pancreas for the verification of malignant tissue of the pancreas, as well as the high risk of developing pancreatic cancer in complicated and clinically manifest

forms of chronic pancreatitis, has been proven.

3. Using all the described methods of pre- and intraoperative diagnostics, it was possible to optimize the choice of the volume of surgical intervention in complicated forms of chronic pancreatitis in patients with a high risk of developing pancreatic cancer. The obtained results improved the quality and extent of the surgical interventions performed.

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**ОПТИМІЗАЦІЯ ВИБОРУ ОБ'ЄМУ ОПЕРАТИВНОГО ВТРУЧАННЯ ПРИ ВИРАЖЕНИХ МОРФОЛОГІЧНИХ ТА СТРУКТУРНИХ ЗМІНАХ ПАРЕНХІМИ У ПАЦІЄНТІВ З ВИСОКИМ РИЗИКОМ РОЗВИТКУ РАКУ ПІДШЛУНКОВОЇ ЗАЛОЗИ**

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*Хронічний панкреатит є поширеною рецидивною патологією підшлункової залози. Тривалий перебіг запального процесу, що супроводжується хронізацією, призводить до розвитку раку підшлункової залози. Мета роботи - вивчити морфологічні зміни підшлункової залози у щурів та рівень матриксних металопротеїназ і тканинного інгібітора металопротеїназ у пацієнтів з ускладненими формами хронічного панкреатиту та високим ризиком розвитку раку підшлункової залози для оптимізації вибору об'єму оперативного втручання. Проведено гістологічне дослідження підшлункової залози щурів із хронічним панкреатитом та хронічним панкреатитом на фоні цукрового діабету. Обстежено 27 пацієнтів, прооперованих впродовж 2020-2022 рр. З них у 15 чітко та переконливо віддиференціювати хронічний панкреатит від раку підшлункової залози ми не змогли, тому що досить часто клінічні симптоми та діагностична картина цих захворювань практично однакова. У решти 12 пацієнтів хронічний панкреатит був підтверджений усіма притаманними клінічними ознаками та наявною протоковою гіпертензією. Проведено дослідження матриксних металопротеїназ (MMP-1, -2, -3, -8, -9, -10) та тканинного інгібітора металопротеїназ. Отримані результати були оброблені статистично. Морфологічні зміни підшлункової залози у щурів відповідають високій і помірній дисплазії протоки класу PanIN 2 і PanIN 3, що є прямими предикторами аденокарциноми підшлункової залози. У 22 пацієнтів встановлена екзокринна недостатність середнього та важкого ступенів, підтверджена значним зниженням фекальної еластази. Була проведена інтраопераційна біопсія зміненої тканини підшлункової залози. Серед 15 прооперованих пацієнтів основної групи у 9 діагностували цукровий діабет, зміну MMTs та пептидного пулу, що притаманно малігнізованій тканині. Інтраопераційно після проведення панч-біопсії у 3 пацієнтів виявлено ацинарну метаплазію, у 4 - зміни у тканині, характерні для PanIN2-PanIN3, у 3 - інтраопераційно підтверджений рак підшлункової залози у ділянці головки. Зміни у білковому профілі плазми, клінічні прояви, а також характерні зміни у тканині підшлункової залози давали підстави для виконання розширених резекційних втручань. Вивчення морфологічної структури підшлункової залози, застосування якомога більше методів для диференційної діагностики між хронічним панкреатитом та раком підшлункової залози, а також комплексний підхід до пацієнта дозволить виконати найбільш правильне та ефективне втручання.*

**Ключові слова:** *підшлункова залоза, морфологічні зміни, хронічний панкреатит, фіброз, протокова аденокарцинома підшлункової залози.*

**Author's contribution**

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