Pancreatic cancer: terra incognita in modern gastroenterology

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Definition. Pancreatic cancer is a malignant tumor that develops from epithelial tissue of different parts of the pancreas. Mostly pancreatic cancer localized in the head (63.8%), rarely affects the body (23.1%) and the tail of the pancreas (7.1%) [3, 8, 12, 35].

Histologically, pancreatic cancer is the most common adenocarcinoma (80%), developing from ductal epithelium, with varying degrees of cellular differentiation; rarer acinar cell carcinoma of the pancreas, which is localized mainly in the body and tail of the pancreas [2, 14, 36].

Prevalence. Epidemiological studies indicate that the cancer of the pancreas takes in different countries 7-10th place among oncological processes of various localization and 0.7% of malignant tumors of the digestive system [27]. Pancreatic cancer is diagnosed more often in men (in a ratio of 1.2-1.3:1), preferably in the age of 60-80 years. Very often it is common in the industrialized countries of Europe (mostly in the Nordic countries) and North America [27, 49].

Features of the pancreatic cancer are 1) long hidden course; 2) non-specific late manifesting clinical symptoms that mimic chronic pancreatitis (CP); 3) emergence in the early stages of tumor metastases; 4) tendency of multicentric tumor growth; 5) low sensitivity to chemoradiotherapy; 6) limited possibilities of morphological diagnosis (biopsy).

These features of pancreatic cancer due to the fact that at the time of his diagnosis in 40% of patients already have distant metastases of cancer, due to which their life expectancy after diagnosis is not more than 6 months, 30% of them die within the first month. The survival of patients with pancreatic cancer in the first year after diagnosis is not more than 8%, and for 2-5 years — 1.5-5%.

The early stage of pancreatic cancer can be diagnosed in no more than 3.8% of the cases [1, 15, 16, 39].

The incidence of pancreatic cancer in different countries varies from 2,2-4 to 11-12,5 cases per 100 thousand people, including 9.7 for men, and for women — 7.7 per 100 thousand. In the United States 37 thousand cases of pancreatic cancer are diagnosed annually, 33 thousand of them die within a year; annual mortality rate in Europe is 40 thousand. [35]. In Russia, the incidence of cancer of the pancreas reaches 8.8 cases per 100 thousand of population.

Perhaps the ethnic factor matters. For example, U.S. pancreatic cancer incidence in African Americans is 2 fold higher than in Europeans [49].

It is important to emphasize that in the last 50 years the incidence of pancreatic cancer has been steadily increasing (in England in this period it has grown 3 times), and the mortality rate has a downward trend.

Thus, pancreatic cancer remains one of the unsolved problems of gastroenterology [11, 49]. It is no coincidence N.A. Skuja called it ***"insidious invisible"*** [16]. We propose to call the cancer of the pancreas ***«terra incognita of modern gastroenterology"***.

The etiology and pathogenesis of pancreatic cancer has not yet been established, so usually do not discuss the etiological factors and risk factors (RF), increasing the likelihood of its development [49].

One of the most proven risk factors of pancreatic cancer is ***chronic pancreatitis*** (CP), which for a specific reason can be considered as a precancerous disease [17, 46, 63].

In clinical studies carried out by methods EBM, it was found that in 17% of pancreatic cancer it develops in patients suffering from long-term CP [5, 48, 71]. In the long-term course of CP ,risk of developing pancreatic cancer increases 20 times, and in such form it, as ***hereditary CP —*** 60 times [17]. Analysis of anamnestic data in patients with pancreatic cancer showed that a large proportion of cases was preceded by CP. Thus, observed from the long CP 1552 patients over 10 years have

developed pancreatic cancer 29 (16.5%), which is much higher (15-16 fold) than in the general population [2, 3, 12, 39].

Particularly noteworthy are the patients with ***hereditary CP*** of autosomal-dominant inheritance, which was first described in 1957. This form of CP is characterized by the fact that it usually develops at a young age, and in 55-60 years in 40-53% of cases occur in its transformation of pancreatic cancer. It has been suggested that this contributes to early onset of clinical manifestations of CP and duration of the inflammatory process in the pancreas [9, 10, 31, 40, 52].

Another form of CP, prone to tumor progression is a ***tropical pancreatitis*** (kwashiorkor) in children in the developing tropical Africa and India in chronic starvation protein that also has ancestral roots. Tropical CP often takes place with exocrine pancreatic insufficiency, and diabetes mellitus (DM). As has been established, long flowing diabetes increases the risk of pancreatic cancer by 50-100%, although the mechanism of this process is not clear [66]. The clinical manifestation of diabetes usually precedes the development of pancreatic cancer for 5 years or more [12].

Cystic fibrosis (CF) is a hereditary disease with autosomal recessive mode of inheritance, in which pancreatic failure occurs in utero due to gene mutations CF Download now, which was isolated in 1989; in subsequent years it has been deciphered and structure [7, 19]. Upon CF occurs CFTR mutation, which transmembrane conductance regulator, which leads to changes in the calcium-dependent regulatory protein violation fluid transport in the protein substrate pancreatic juice, resulting in a thick viscous abnormal secret impedes its progress on the pancreatic ducts, and there they obstruction; there is destruction of ductal and acinar epithelium and then their replacement by fibrous tissue; develops cystic fibrosis of the pancreas [7, 25]. CF proceeds with exocrine pancreatic insufficiency from birth.

When CF risk of developing pancreatic cancer increases by 5-10 times, and diagnose it as early as 40-45 years of age [2, 5, 39, 71].

When all of these clinical forms of CP preceding the development of pancreatic cancer, it is possible to note the ***presence of genetic determinism*** [25, 50, 60].

Thus, when there is a hereditary CP PRSS1 gene mutation encoding cationic trypsinogen; also indicates BRCA2 gene mutation that increases susceptibility to pancreatic cancer [3, 10]. Upon tropical CP ***cathepsin B*** gene polymorphism is recorded, and at CF — CFTR gene mutation, which has already been mentioned, and R334W-**reHa** [19, 24].

The role of heredity in the development of pancreatic cancer is evidenced by the fact that blood relatives of patients with pancreatic cancer (first-degree relatives), increased risk of developing cancer in the 3-18 times, and therefore it is recommended to call ***familial pancreatic cancer,*** thus, as it was found locus susceptibility to pancreatic cancer is located on chromosome 4Q32-34 [41, 67].

The carcinogenesis of cancer of the pancreas involves ***tumor suppression gene: K***-ras, p53, etc. [51, 55, 56]. With their inherent oncogenic mutation lost their role in regulating cell proliferation processes, differentiation and apoptosis.

Important risk factors of pancreatic cancer is ***the duration of the inflammatory process in the pancreas*** (CP) [40, 52] and ***oxidative stress,*** damaging the cell's genome with the development of point mutations that contribute to the oncogenic transformation of CP [4, 54].

The description of ***histological signs of precancerous lesions*** (malignancy) in the pancreas, which received the name ***pancreatic intraepithelial neoplasia — PanIN*** They can be subdivided into three ***groups:*** PanIN-h at which the intraepithelial ductal ***hyperplasia; PanIN-2*** — low-grade dysplasia and ***PanIN-3*** — evident ductal epithelial dysplasia and/or adenocarcinoma [5, 71].

Data have been recently published on a possible role in the development of pancreatic cancer viral hepatitis B. It has been shown that a chronic carrier state HBsAg+ and less HBV increases the risk of pancreatic cancer, particularly in those cases where there is a history of diabetes in patients. Synergy was observed between the carriage of HBsAg+ and the development of pancreatic cancer, especially in diabetes sufferers at the same time.

The basis for this assumption was the information that the DNA of hepatitis B virus and its antigens can be localized (replication) in the prostate tissue, promoting the development of CP. Thus, chronic hepatitis B carrier state and an inactive HBsAg+ can be considered as RF pancreatic cancer, the presence of diabetes and has a synergistic effect on the process [10, 44].

Among of exogenous RF of pancreatic cancer in the first place is ***smoking,*** in which the frequency of pancreatic cancer increases by 2-3 times, depending on the number of cigarettes smoked and duration of smoking. Failure of hard-core smokers from smoking reduces this risk by 30%. It is believed that up to 25-33% of cases of pancreatic cancer associated with smoking [1, 3, 16, 22].

Another RF is ***excessive consumption of animal fats and meat products,*** especially fried and smoked that contain carcinogens (tetracyclic amines and polycyclic aromatic hydrocarbyl). Some authors considered to cancer risk factors RV systematic use of ***strong coffee and concentrated alcoholic beverages,*** but the evidence of carcinogenicity is inadequate [17]. However, be aware that long-term alcohol abuse is one of the major etiological factors of CP, which is recognized as a precancerous condition, so the intake of alcohol should be avoided.

As the pancreas cancer risk factors may also serve ***some of the chemical compounds*** (benzidine, chlorohydrin, acrylamide, etc.), which are chemical carcinogens. Therefore, workers of chemical plants, long-term contact with them are at risk of developing pancreatic cancer [2, 3, 8, 12, 14, 35].

Clinical picture. In the early stages of development of the pancreatic cancer is asymptomatic (latent) for the disease. The appearance (manifestation) of clinical symptoms usually indicates the already widespread tumor process with the presence of regional, and in some cases, and distant metastases.

Specific (pathognomonic) of symptoms of cancer of the pancreas is not. Its clinical symptoms are indistinguishable from the original active symptoms of CP. Patients concerned about pain in the upper abdomen radiating mostly backwards — towards the loin; less pain spreads to the left in a left-hand polupoyasa, even more rarely acquires the character of shingles. Pain is usually stored around the clock, are

amplified at night. At the same time there are dyspeptic symptoms: decreased appetite until anorexia (V.H. Vasilenko named it anorexia pancreatica) [1]: during 2-3 months patient loses 10-20 kg; nausea and vomiting appear, do not bring relief, etc.

An important step, indicating the progression of the pathological process, is the appearance of jaundice, which has a mechanical (obstructive) character, followed by a painful skin itching, dark-colored urine (the color of beer) and discoloration of feces. Jaundice indicates the tumor process lesion pancreas head, through which the distal portion of the common bile duct [1, 3, 5, 15, 35, 36].

Anicteric form of pancreatic cancer occurs in 10-40% of cases.

In some patients with cancer of the pancreas it is possible to palpate the dense fixed tumor in the pancreas projection on the anterior abdominal wall. In the presence of metastatic cancer in the liver can be palpated enlarged (hepatomegaly) thick and lumpy liver. Further there ascites, portal hypertension due to developing and/or associated with cancer metastasis according to the peritoneum [1, 8, 14, 16].

On palpation of the gall bladder (gallbladder) is defined symptom Courvoisier-Terje: increased painless gallbladder due to the blockade of the outflow of bile into the duodenum and overflow it DGP.

In some cases jaundice complicated by cholangitis; the appearance of signs of intoxication and liver failure, which are accompanied by pain in the right upper quadrant. Rapidly progressive signs of exocrine pancreatic insufficiency, broken processes of digestion and absorption in the small intestine (syndrome maldigestion and malabsorption), there is diarrhea with the release of large amounts of loose stools gray, containing a significant amount of non-cleavage of fat, with sharply fetid odor ("pancreatic feces") [1, 4, 16]. There may be signs of diabetes.

In end-stage pancreatic cancer jaundice becomes dark yellow-green, almost black color (melas icterus) and cachexia observed.

Diagnosis. In connection with the recognition of the importance of pancreatic cancer in the early stages of its development should be used for this purpose the entire arsenal of modern laboratory and instrumental diagnostic methods.

Laboratory diagnostic methods. In general blood test for cancer of the pancreas is observed leukocytosis with nuclear shift to the left, increasing the ESR.

In the biochemical analysis of blood is determined Dysproteinemia with increasing α- and γ-globulin fractions of serum proteins; Early increase in enzymes of cholestasis (alkaline phosphatase, gamma-GTP and PAWS), a moderate increase in cytolytic enzymes (ALT, AST).

In the study of exocrine pancreatic function (test with elastase-1), there is increasing its reduction; phenomenon appears "deviation of pancreatic enzymes in the blood" with increasing levels of amylase and lipase in blood serum trypsin (type of obstructive pancreatic secretion) and increase their urinary excretion of [3, 4, 16, 18].

Biomarkers of pancreatic cancer may be oncogenic genes tumor suppressor: K-ras, p53, p16, DPC4, as well as increased activity of telomerase, which is an RNA-dependent DNA polymerase [9, 25, 51, 57, 58]. Their oncogenic mutations potentiate tumor process in the pancreas, "un-braking" mechanism of carcinogenesis [57].

Mutations in K-ras gene at codon 12 occur; cancer of the pancreas is found in pancreatic juice and bile in patients. It is believed that K-ras gene encodes a protein homologous to transforming growth factor (TGF). Described oncogenic K-ras mutations at codons 13 and 61 of ras-protein, which is specific for pancreatic cancer.

However, oncogenic K-ras can be found not only in pancreatic cancer, but (much less) and CP. For example, mutations K-ras gene are determined by CP to 13%, while the pancreas cancer — 80-90%, in connection with which it is regarded as "genetic marker for pancreatic cancer" [51, 55, 56]. This fact, some authors regard as confirmation of the pathogenetic link between CP and the development of pancreatic cancer [51, 56].

Oncogenic mutations of tumor suppressor genes p53, p16, and DPC4 may also be used in the diagnosis of pancreatic cancer.

The p53 gene is called the ***"guardian of the genome",*** but it is subject to an oncogenic mutation, resulting in inhibited apoptosis, and genetically modified cells begin to multiply uncontrollably, their differentiation is disturbed, which increases the likelihood of developing pancreatic cancer. Thus, the p53 gene is a tumor

suppressor, becomes the ***"Achilles' heel" of the anti-tumor protection.*** In pancreatic cancer, its mutation is found in 70% of cases [25, 41, 58].

Gene DPC4 (deleted in pancreatic cancer, "destroying cancer"), localized to chromosome 18; It mediates transforming growth factor TGF-β and p16 gene. Its oncogenic mutation by 40% increase in the risk of pancreatic cancer, but it is possible and in cancer of other sites (colorectal cancer, gastric cancer), in connection with which it is often referred to as ***"family cancer marker"*** [4, 17, 25, 41]. Mutations in the p16 gene are associated with pancreatic cancer in 40% of cases [57].

The gene MMR (mismatch repair gene) is responsible for DNA replication. His mutations (defects) lead to accumulation of errors of DNA in the genome, primarily in the genes that convert receptors transforming growth factors (TGF-α and TGF-β) [61].

Upon pancreatic cancer ***increase telomerase activity*** is observed in cells in cancer and pancreatic juice where its level is usually increased. However, according to most authors, the definition of telomerase for diagnosing pancreatic cancer is inappropriate [61, 65].

Some importance in carcinogenesis of cancer of the pancreas is given ***protein molecules secreted by pancreatic stellate cells.*** CD10 and CD271, which can act as a "target" for cell-specific therapies for cancer of the pancreas [28, 34, 45, 62].

For the diagnosis of pancreatic cancer ELISA methods of RIA are also used ***in the determination of serum tumor marker*** CA 19-9 (carbohydrate antigen) and CEA (carcinoembryonic antigen). The upper limit of normal for CA 19-9 is 37-40 units/mL, for CEA — 10-15 ng/ml. Upon pancreatic cancer CA 19-9 levels increased to 556 ± 13,4 U/ml, and the presence of distant metastases — 1000 U/ml or more (the sensitivity of determining — 90%, but specificity is significantly lower as it rises and at other cancer sites).

CEA content increases in pancreatic cancer (10 times or more) in 64% of patients, but it is even lower specificity than CA 19-9. Increased CEA levels are considered more specific to colorectal cancer than for pancreatic cancer [6, 26, 70].

Recently, the search is conducted ***more reliable biomarkers for the diagnosis of pancreatic cancer,*** which could help in detecting tumorous processes in the early stages of its development.

Thus, it was shown that increases pancreatic cancer gene expression and S100 family MUC [68, 69].

S100 family of proteins related to low Ca^{2+}-bound proteins, influencing the course of intra- and extra-cellular processes such as cell proliferation, cell differentiation and intracellular signaling.

It has been found that with pancreatic cancer at early stages of its development observed increased excretion of protein S100 (most frequently — S100P protein) that can be quantitatively and qualitatively identified [68, 69].

MUC family proteins are glycoproteins with high molecular weight. In cancer of the prostate occurs overexpression of MUC1 and MUC6 proteins in tumor tissue. Material for the study was prepared by aiming aspiration biopsy of the prostate tissue in the proposed development of the tumor area (under ultrasound guidance). It is not yet developed a method of quantification [29, 65, 69]. These studies offer hope for the possibility of an early (early) diagnosis of pancreatic cancer in the near future.

Diagnostics to recognize pancreatic cancer is currently using ultrasonography (US), including endoscopic ultrasonography (EUS); computed tomography (CT); Magnetic resonance imaging (MRI); fibrogastroduodenoscopy (EGD); angiography; endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MR-CPH) fine-needle aspiration biopsy of the prostate (controlled by EUS), and others.

The aim of research — visualization of the tumor, determine its location, size, lesion length, degree of differentiation, the presence of metastasis (regional and distant), morphological verification of the tumor and to determine its stage.

When ultrasound (especially when EUS) you can set the size of cancerous tumors in the pancreas, involvement in tumor vascular process of feeding the pancreas (arteries and veins), as well as the adjacent organs (liver, gall bladder, duodenum) [2, 8, 12, 13, 35, 37, 38].

Some authors recommend conducting intraoperative ultrasonography using special sensors operating in real-time [15], which allows you to specify the diagnosis and determine the resectability of the tumor.

For the purpose of differential diagnosis of pancreatic cancer and pseudotumor ("head") CP uses a technique of three-dimensional reconstruction of ultrasound images of the prostate in 3D mode. This method allows visualization of even smaller tissue formation in the pancreas, to establish a relationship of cancer to adjacent organs and blood vessels with a detailed study of blood flow in arteries and veins that supply the pancreas, thanks to the three-dimensional image of the vasculature [13].

CT, combined with contrast, allows to specify the size (1 cm or more) and the shape of the tumor in the pancreas, its topographic and anatomic location, structure and thickness, to consider in detail the head of the pancreas, its body and tail. Especially informative MRI in poorly differentiated cancer of the pancreas, where it can help to establish deterioration of pancreatic perfusion, its contrast and the presence of contrast rim [59].

Some authors have used for early diagnosis of cancer of the pancreas ***positron emission tomography*** — PET, the recording power of the two oppositely directed gamma rays, which are a result of ***annihilation*** (the interaction of positively and negatively charged particles and their qualitative transformation in the photon) allow visualize initial signs of pancreatic cancer study was carried out with glucose isotope, which are known to accumulate in tumor tissue (sensitivity — 96%, specificity — 100%) [15].

In recent years, it was developed and introduced into clinical practice ***technique multislice contrast CT.*** Scanning the prostate is performed in arterial and venous phase, which allows us to consider the celiac trunk, the superior mesenteric artery and the portal, splenic and mesenteric veins, to establish the presence of metastases in the liver.

Another type of CT — ***hydro-CT*** in which to improve the visualization of the pancreas is introduced into the stomach of 1-1.5 liters of water, causing it to stretch and stomach hypotension provide preliminary appointment Buscopan [42].

The main features of pancreatic cancer when imaging using ultrasound and CT is the presence of bulk formation in the pancreas tissue structure (determine its location, size, prevalence of tumor process, etc.).

In cancer of the pancreas is often determined by the increase of its head, acquiring a rounded shape; it accumulates bad contrast, a tumor is formed around a contrasting rim. Determined by tumor invasion into the adjacent artery and vein; penetration of adjacent organs; affected regional and distant lymph nodes [2, 12, 14, 15].

ERCP is an additional invasive method for diagnosing pancreatic cancer. Used primarily in the defeat of the head of the pancreas and its duct system. As the head passes through the gland, the distal part of the common bile duct, ERCP allows you to install the obstruction; you can also take a biopsy of duodenal wall, adjacent to the head of the pancreas.

Conducting ERCP in some cases (5-15%) can cause serious complications, up to acute pancreatitis, therefore prefer safe and non-invasive diagnostic method, in recent years — MR CPH, which can be regarded as the *"**method of choice"*** [4, 12].

Percutaneous transhepatic cholangiography is mainly used in the lesion of cancer of the pancreatic head to determine the level of mechanical obstruction of the common bile duct, the completeness of its blockade of tumor originating from the pancreas. Defined in this stump common bile duct has a conical shape and jagged edges.

Test (diagnostic) laparoscopy and laparotomy is not possible to examine the prostate, but it can be useful, as they give an opportunity to see even small metastases of cancer of the pancreas on the peritoneum and take to study ascites. This method is not indifferent to the patient, so it is only on the strict condition can be used.

Fine-needle aspiration biopsy of the affected pancreas cancer (25 G needle diameter) is performed under ultrasound (EUS). It provides morphological verification of the diagnosis of pancreatic cancer and allows you to set its histological form.

According to ***morphological classification of*** pancreatic cancer (Y. Solcia et al., 1997) distinguishes [47] following:

I. ***Exocrine pancreatic cancer.***

1. Ductal adenocarcinoma of the pancreas (5 microscopic forms).
2. Giant pancreatic cancer.
3. Serous cytoadenocarcinoma.
4. Mucinous cytoadenocarcinoma.
5. Intraductal papillary-mucinous adenocarcinoma.
6. Acinar cell carcinoma of the pancreas.
7. Pancreoblastoma.
8. Solid pseudopapillary pancreatic cancer.
9. Cancer of the pancreas of mixed type.

II. ***Endocrine pancreatic tumors.***

1. Insulinoma.
2. Gastrinoma.
3. Vipoma.
4. Glucagonoma.
5. Somatostatinoma and others.

III. Low-grade (small cell), pancreatic cancer [4].

For preoperative evaluation of pancreatic cancer stage it is advisable to use the classification of the TNM (T — ***tumor,*** of N — ***nodus,*** M — ***metastasis*** *)* [71]:

T_x — primary tumor can't be assessed;

T_0 — no evidence of primary tumor;

T_{is} — ***cancer in situ;***

T_1 — tumor within the pancreas, diameter <2 cm;

T_2 —tumor within the pancreas, diameter >2 cm;

T_3 — tumor grows beyond the pancreas; its diameter >2 cm;

T_4 — tumor invades the celiac trunk or superior mesenteric artery;

N_x — lymph nodes can't be assessed;

N_0 — metastases to regional lymph nodes are absent;

N — metastases to regional lymph nodes;

M_0 — no distant metastases;

M_1 — there are distant metastases.

In determining the operability of pancreatic cancer using UICC system.

Stage 0 (T_{is}, of N_0, M_0) — carcinoma ***in situ conservation*** (operable);

Stage 1A (T_1, N_0, M_0) — local resectable tumor;

Stage 1B (T_2, N_0, M_0) — local resectable tumor;

Stage 2A (T_3, N_0, M_0) — local invasive resectable tumor;

Stage 2B (T_3, N_1, M_0) — locally invasive, relatively resectable tumor;

Stage 3 (T_4, N_1, M_0) — locally common, relatively resectable tumor; inoperable;

Stage 4 (T_4, N_1, M_1) — inoperable tumor (palliative treatment) [42].

Treatment. The only effective treatment for pancreatic cancer is radical surgical removal of the tumor and its metastases. However, at the time of clinical manifestation operability does not exceed 15-16% [8, 14, 35].

It is accepted to distinguish operable, relative operable, inoperable and metastatic cancer of the pancreas [11].

An international research team surgery *(ISGPS)* recommends that multicentric cancer lesions of the pancreas to produce a complete (total) pancreatoduodenectomy and standard lymphadenectomy [32, 33].

Involvement in the process of tumor of the celiac trunk, the upper mesenteric and hepatic arteries indicates unresectable pancreatic cancer.

To improve long-term outcomes in patients undergoing pancreatectomy may be carried out vascular or arterial multivisceral resection in specialized surgical centers [23, 30].

The presence of metastatic cancer to regional lymph nodes worsens prognosis and is an indication for the standard lymphadenectomy [33].

Some surgeons with advanced cancer of the pancreas perform combined pancreatectomy combined with resection of choledoch and distal stomach [29].

Postoperative mortality is 15-30%, and the patients survived after surgery, live an average of 17-20 months.

In the presence of jaundice, you must first restore the flow of bile (bile ducts carry out decompression) and to reduce the level of bilirubin in the blood up to 70 mmol/l, and only then to carry out radical surgery for pancreatic cancer.

In cases where the conduct radical surgery is not possible, run a variety of ***palliative surgery.*** So, if you have jaundice overlay bilidigestive anastomosis; percutaneous transhepatic drainage of the bile ducts; endoprosthesis of the biliary tract; endoscopic papillosphincterotomy and others.

After the operation, as well as in the case of inoperable cancer of the pancreas is prescribed ***adjuvant therapy***, perform an important supporting role.

The European Study Group for the Study of Pancreatic Cancer (ESPAC) recommended as the most effective means of treating pancreatic cancer adjuvant ***monotherapy by gemcitobine*** as an intravenous infusion at a dose of 500-2500 mg/m^2 slowly (within 60-80 minutes). Antitumor effect gemcitobine due to its cytostatic effect related to the inhibition of DNA synthesis in tumor cells. Intracellular metabolites of gemcitobine incorporated into the DNA chain, causing a complete blockage of DNA synthesis and programmed death of cancer cells [47, 53, 64]. Upon using gemcitobine, a significant increase is noted in survival rate and reduction in the number of tumor recurrence after surgery.

Traditional medicines of adjuvant therapy of pancreatic cancer use 5-fluorouracil (5-FU) in combination with folate drugs (leucovorin). ***5-FU*** is administered by slow intravenous injection of 5 ml of 5% solution (250 mg) daily for 5 days, and ***leucovorin*** — intravenous injection of 20 mg/m^2 followed by transfer to a long-term intake (tablet 1 mg, up to 6 months). The effectiveness of the combined treatment of 5-FU and the folic acid is comparable with the effect of gemcitobine, but they are more toxic. 5-FU can also be combined with a ***platinum drug — cisplatin*** 20 mg/m^2 for four days in the first and fifth week of treatment. Furthermore, the anticancer drugs used ***streptozotocin,*** which is administered intraarterially at 1.5 g/m^2 (in combination with 5-FU); ***doxirubicin*** (30 mg/m ^{2} intravenously daily for 3 days)

and ***immunomodulator galavit*** (100 mg/day) for 5 days before and five days after surgery.

In locally advanced cancer of the prostate is performed ***external radiation therapy,*** which helps to reduce the size of the tumor, but it is more toxic and less effective than monotherapy by gemcitobine. Therefore increasingly using combined chemoradiation therapy and immunochemoradiation therapy.

Unfortunately, standard regimens of chemotherapy and radiotherapy have not yet been developed, and their performance does not exceed 15-28% [20, 21, 43, 53, 64].

Problems of timely diagnosis of pancreatic cancer and effective treatment are still waiting for being solved.

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Pancreatic cancer: terra incognita in modern gastroenterology

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Key words: pancreatic cancer, classification, risk factors, clinical features, diagnostics, treatment

The author presents definition of pancreatic cancer (PC), epidemiological data on its prevalence, risk factors (chronic pancreatitis, viral hepatitis B, smoking, etc.), and clinical symptoms. Modern laboratory and instrumental differential diagnostic methods are discussed. Morphological classification and stages of the neoplastic process are considered with special reference to the methods of its surgical treatment and adjuvant therapy.