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MATHEMATICAL MODELS OF DIFFERENTIAL DIAGNOSTICS AND PROGNOSIS IN CHRONIC PANCREATITIS AND CANCER WITH A PRIMARY LESION OF THE PANCREATIC HEAD

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Abstract

Background. Differential diagnostics of chronic pancreatitis and the pancreas cancer with prevalent affection of head is on of the most difficult and important problems of surgical pancreatology.

Methods. Analyzed the results of surgical treatment of 132 patients, including 68 - for cancer of the pancreatic head (in 46 - with jaundice) and 64 - chronic pancreatitis (CP) with a primary lesion of the pancreatic head (16 - with jaundice). The distribution of patients into groups was carried out with a maximum value of classification functions calculated by special formulas. Next studied indicators of endothelial dysfunction for differential diagnosis.

Results. It was defined the threshold of VEGF = 346 pg/ml, which shared the group of chronic pancreatitis or cancer of the pancreatic head, which was determined based on the Pareto criterion. This model sensitivity was 72.1% and specificity of 75% for the overall accuracy of 72.7%. Even more precision indicator was on the threshold of VEGF = 248 pg/ml, which compared groups of patients with cancer and software of the control group (125.9 pg/ml) and the sensitivity was 86.8%, specificity 82.4%, and overall accuracy of 82.3%. At about the same accuracy had this test and the comparison group of patients with chronic pancreatitis and control: sensitivity 84.4% and specificity of 76.5% overall accuracy

of 81.5% in the threshold VEGF of 155 pg/ml (p<0,05). To develop a prognosis of a pathological process, along with the use of diagnostic data used a method of classification trees. The model showed that the index VEGF is the criterion that discriminates for pancreas-pancreatic cancer-pancreas, but relative differences in the presence of jaundice in patients defined using S-nitrozothiol. The accuracy of the proposed method of prediction was 89%, the price of cross-checking – 82,6% (p<0,05). Pancreatoduodenal resection for Whipple was performed in 23 patients, for Traverso-Longmire - in 8, subtotal right sided pancreatectomy for Fortner - in 3, hepaticojejunostomy by Roux - in 8, duodenopreserving resection for Beger - in 6, her Bernese option - in 7, operation Frey - in 51. In 26 (19.7%) patients, minimally invasive intervention for removal of bile were spread through the final primary pathological process and severe general state. Postoperative complications occurred in 18 (13.6%) patients, died 3 (2.3%).

Conclusion. Constructed mathematical models of differential diagnosis and prognosis allow with the high accuracy detect cancer in the presence of the volumetric formation on the head of pancreas. Along with the using of clinical laboratory and instrumental data to decide the issues of the head's pancreas cancer and chronic pancreatitis diagnostic can be used the proposed method for constructing the classification trees, whose accuracy was 89%, the price of cross-checking – 82.6%, which can be considered as good indexes of the model .

Keywords: **chronic pancreatitis; cancer of the pancreatic head; differential diagnosis; mathematical models.**

Intoduction

One of the tasks of modern surgical gastroenterology is not only supplying of good and perfect direct results but creating facilities for patients' rehabilitation on the early postoperative period and prevention postoperative complications at patients, who had radical operation on the pancreas, because of the chronic pancreatitis (CP) and the pancreas cancer (PC) with prevalent affection of head of pancreas. Traditional tactics of patients' treatment with such pathology not always satisfies surgeons' requirements. It is necessary to improve not only the methods of diagnostics, treatment and prophylaxis of postoperative complications but implementation of new methods, which are based, first of all, on studying of pathogenesis and prognosis of these diseases. Differential diagnostics CP and the PC with prevalent affection of head is on of the most difficult and important problems of surgical pancreatology [1, 2, 3]. The special importance of this problem is connected due to the fact that the PC,

which is discovered at patients, who suffer from CP, is considered nowadays as a precursor of cancer [1, 2]. A low level of PC discovery on the background of CP in the resectable phase shows on the insufficiency of the present algorithms and programs of differential diagnostics of this category of patients. Last decades were widely implemented to the clinical practice such modern methods of diagnostics as ultrasonic scanning (US), endosonography, multi spiral computer-aided tomography (MSCT), magnetic resonance image (MR-image), endoscopic retrograde cholangiography (ERC), percutaneous puncture of P under the control of US or CT with further research of derived gland's tissue, aspiration of pancreatic juice, using of tumorous markers and etc.

Endothelial dysfunction is a pathological condition that occurs on a background of violations production of endothelial factors. This leads to dysfunction of organs and body systems that occur against the background of the imbalance between the production of vasodilator, angiodefensive, angioproliferative factors on the one hand, and the content of vasoconstrictor, prothrombotic, proliferative, on the other. The endothelium is involved in the regulation of vascular tone, vascular permeability, leukocytes and platelets adhesion, angiogenesis, thrombus resistance, immune response, the synthesis of inflammatory mediators and their inhibitors, and also provides barrier functions. An important function of the endothelium is the production of nitric oxide (NO), which supports the basal vascular tone and is involved in vasodilation in response to various stimuli. In recent years, in the scientific literature appeared a large number of studies that show the important role of nitric oxide as a multifunctional regulator of structural metabolic processes [1, 2]. Nitric oxide is equally a potentially toxic molecule that plays a negative role in arterial hypertension, diabetes, neoplasms, neurodegenerative processes, atherosclerosis, liver cirrhosis, kidney disease and other pathological conditions of the system [3]. Recently was received a lot of new data about NO metabolism in living cells and the structure of NO synthase. It was established that nitric oxide works as an important regulator of cellular processes such as a genetic expression and functional activity of mitochondria. In the organism NO is synthesized with the amino acids L-arginine. This process is a complex oxidative reaction which is catalyzed by the enzyme of NO synthase, which is reminiscent of multifunctional oxidoreductase and resembled by the number of properties a system of cytochrome P_{450} reductase [3].

Nowadays was identified three isoenzymes NoS, which are named according to the type of cells, in which they were first discovered [1, 2, 3]; neuronal (nNoS), inducible (iNoS) or macrophage (mNoS) and endothelial (eNoS). All NoS isoforms catalyze the formation of NO in response to receptor, chemical, biological or physical stimulation. To consider all

written above, **the aim of this work** was to study the role of endothelial dysfunction in the mechanism of CP formation and a PC with prevalent affection of head of pancreas, development and implementation of mathematical models of differential diagnosis and prognosis at these diseases.

Materials and methods. The results of surgical treatment of 132 patients and basic clinical and laboratory characteristics were analyzed and presented in table 1. All patients were divided into 5 groups: the first – control (conventionally healthy, n=17), the second – patients with CP without jaundice (n=48), the third – patients with CP with jaundice (n=16), the fourth – patients with PC without jaundice (n=12), the fifth – patients with PC with jaundice (n=56). To all patients were performed the general clinical laboratory methods of blood and urine tests, biochemical blood tests; to the most patients was performed the test on tumor markers CA 19-9. The program of research of endothelial dysfunction at patients with CP and a included: determination in blood serum of patients and conventionally healthy patients of oxidation products of nitric oxide – nitrites (NO_2), nitrates (NO_3), S-nitrosothiol, endothelial (eNOS) and inducible (iNOS) NO-synthase, and also for one from the toxic products of oxidative deaminization of amino acids (L-glutamine and L-asparagine) purine nitrous bases – ammonia (NH_3). The content in blood serum of NO_2, NO_3, S-nitrosothiol and activity of eNOS and iNOS was determined in accordance with recommendations [4]. The ammonia in the blood serum was determined by the method of ionic-metabolic chromatography ionites. After dividing of amino acids on ionites, the registration of their number and ammonia was carried out by automatic analyzer amino acids T-339 (made in Czechoslovakia).

To research the concentration of vascular endothelial growth factor (VEGF) patients' blood was taken in the morning before meal from cubital vein for plasma without additives and within an hour after taking the tube with blood was delivered to the laboratory for further processing. VEGF concentration in blood plasma was determined with using the set of reagents for solid-phase immune-enzyme analysis «Human VEGF Quantikine ELISA» (made by the company «R & D Systems», USA). We used the following instrumental methods, ultrasound scanning (US), multispiral computer-aided tomography (MSCT) (with/without contrasting), endoscopic esophagogastroduodenoscopy (EEHDS), endoscopic retrograde cholangiography (ERC), magnetic resonance image (MR-image) video laparoscopy, puncture biopsy under ultrasound scanning.

Static handling of given results of the research with the using of the method of variation statistics was made by the programme "Biostatistics". Differences between samples were considered statistically significant at the value for $p<0.05$.

Table 1

Clinical and laboratory characteristics of patients (Me (Q_1–Q_3))

Index	Chronic pancreatitis with a primary lesion of the pancreatic head (n=64)	Cancer of the pancreatic head (n=68)	P
Age	52.2±2	61.5±1,4	p=0.00024
Male/female	53/11	48/20	p=0.206
IMT, kg/м^2	21 (20-26)	24 (21-28)	p=0.537
Pain	64	12	N
Jaundice	18	68	N
Exocrine insufficiency of pancreas	58	32	N
Ascites	8	14	N
Symptoms of CNS affection	4	8	N
Blood leucocytes, $\times10^9$/l (4.0-9.0)	9.8 (5.4-11.6)	8.4 (5.5-10.2)	p=0.234
Common bilirubin, mkmol/l (5.0-21.0)	27.4 (16.3-44.8)	87.7(66.4 – 311,3)	p=0.0001
ALT of blood, U/l (before 31)	78.6 (57.9-96.4)	154.6 (68.6-211.2)	p=0.001
AST of blood, U/l (before 31)	67.3 (44.5-88.5)	148.5 (53.2-189.4)	p=0.001
Blood glucose, mmol/l (4.1-5.9)	5.34 (5.3-12,1)	7.05 (5.9-12.3)	N
Blood creatinine, mkmol/l (before 115)	85.4 (76.4-111.5)	97.2 (81.8-123.9)	p=0.043

Results and Discussion. Clinical and laboratory characteristics of patients are presented in Table 1. Development of a mathematical model of differential diagnosis at volume formations of the head of pancreas heads was implemented in some stages. **On the first stage** to distinguish patients with the PC were used 31 clinical-laboratory and instrumental indexes, which were obtained in the first days after the patient arriving to the clinic. **On the second stage** of differential diagnosis (in the preoperative period) indicators of endothelial dysfunction were examined. **On the next stage**, along with the use of diagnostic data, to solve problems of prediction, the method of tree classification was used.

Prediction of diagnosis (pancreas cancer – CP) can be done by different methods of multivariate statistical analysis, the choice of which will be determined by a measuring scale, distribution law and availability of statistical relationships between them. That's why on the first stage it was made the analysis by the method of descriptive statistics. The comparison of reliability differences in indexes of central tendencies for patients with CP and the PC showed that they are not homogeneous in age composition. So, in the group of patients with a PC the age of patients (61.5±1.4) was much more older, than in the group of ones with CP (52.2±2) and the differences were reliable by the criterion of Mann - Whitney U-test ($p=0.00024$). That's why homogeneous groups were formed. They consisted from 47 patients with CP and 53 patients with the PC. The analysis showed that significant ($p<0.05$) differences were detected (of Mann - Whitney U-test) only for 9 indexes, that were researched: segmented neutrophil, lymphocytes, fibrinogene A, total bilirubin and its fraction, blood glucose, albuminuria and diameter of common bile duct.

During building a system of forecasting of probability of the presence of P cancer at patient various statistical methods were considered: a discriminant analysis, a classification tree, a logit regression and others. As the researches showed, the most appropriate method for this data structure was a discriminant analysis. The high accuracy of posteriori classification (Table 2) was achieved, even when were used only three factors: direct bilirubin, lymphocytes and age of patients. The reduction of the number of predictive indicators to three was made because of their multicollinearity (high level of the correlation bonds), for example: general – direct bilirubin – indirect bilirubin – diameter of common bile duct, and the willing to reduce the number of predictors, during keeping the accuracy of the forecast.

Table 2

Accuracy of posteriori classification by discriminant analysis

Pathology	Classification matrix: lines – groups, that were observed; columns – prognosed groups		
	A percent of right matches	CP (amount of patients)	Cancer of the pancreas
CP	74.5%	38	13
PC	82.1%	12	55
Total:	78.8%	50	68

The predicting of probability of the presence of PC at patients was made after calculations of classification functions. Previously selection of the group (CP or PC) was

determined on the base of the detection of maximum classification functions that were calculated by the formulas:

Y_{CP} = –16.75 – 0.0035 × «direct bilirubin» + 0.42 × «lymphocytes» + 0.4 × «age»;

Y_{PC}= –18 + 0.0083 × «direct bilirubin» + 0.36 × «lymphocytes » + 0.44 × «age».

The order of indexes in classification functions corresponds to the contribution of each predictor in the process of classification. The accuracy of the prediction model was tested in the test sample of 20 patients (8 – with PC, 12 – with CP), and the accuracy of a forecasting model was 74%.

Thus, in view of the fact that, patients with CP form a "risk" group of developing PC, the problem of differential diagnosis at presence of volumetric formation mainly in the head of pancreas is relevant for the choice of treatment strategy. To exclude PC in patients with CP on the first stage should be used reasonable mathematical model of differential diagnosis (78.8% overall accuracy), which was developed on the base of on available clinical and laboratory and instrumental criteria.

Table 3

The condition of endothelial disorder at patients with chronic pancreatitis and the pancreas cancer.

Indexes	Observation groups, $\bar{X}$ ±σ.				
	Conditionally-healthy (n=17)	Chronic pancreatitis with a primary lesion of the pancreatic head		Cancer of the pancreatic head	
		Without jaundice (n=48)	With jaundice (n=16)	Without jaundice (n=12)	With jaundice (n=46)
NH3 (nmol/l)	23.1±1.6	36.2±2.6*	38.2±3.4*	47.8±3.2*	59.3±4.2*
NO2 (mkmol/l)	14.7±1.2	21.4±1.3*	25.8±1.7*	28.4±1.6*	35.7±2.1*
NO3 (mkmol/l)	24.6±1.5	31.8±1.5*	40.6±2.3*	46.3±2.2*	57.4±3.7*
S-nitrosothiol (mkmol/l)	0.23±0.02	0.32±0.03*	0.80±0.07*	0.38±0.04*	0.89±0.07*
eNoS (pmol\ min × mg protein)	0.58±0.04	0.77±0.06*	0.95±0.08*	1.04±0.09*	1.23±0.11*
iNoS (pmol\ min × mg protein)	0.38±0.03	0.63±0.05*	0.75±0,06*	0.27±0.03*	0.21±0.02*
VEGF (pg/ml)	125.9±10.6	212.2±9.5*	268.1±16.0*	431,9±22*	872.6±76.6*

A note: *- authentically with control ($p<0.05$).

Results of the research of endothelial dysfunction at patients with CP and PC showed the increasing in blood plasma of nitrites, nitrates, S-nitrosothiol, endothelial (eNoS) No-synthase. At the same time, CP course was accompanied by the increasing of inducible (iNoS) NO-synthase, while the PC course this indicator is significantly reduced comparing to a group of conditionally healthy patients (Table 3). The assessment of endothelial dysfunction indicators at CP was characterized by growth of nitrites on 45,5% and 75,5%; nitrates on 29,2% and 65,0%; S-nitrosothiol on 39,1% and 247,8%; endothelial NO-synthase on 32,7% and 65,5%; inducible No-synthase on 63,7% and 97,3%, according to conditions of disease with and without jaundice.

The analysis of indexes of endothelial dysfunction in PC patients found in the blood serum the increasing of nitrates on 93,1% and 142,8%; nitrites on 88,2% and 133,3%; S-nitrosothiol on 65% and 286,9%; endothelial No-synthase on 79,3% and 112%, on the background of inducible No-synthase on 29% and 44,8%, respectively, at PC course without jaundice and when it is available. The research of condition of No-synthase oxidative system detected the increasing of concentration of ammonia in the blood serum of PC patients more than 2 times. It indicated on the development of endogenous intoxication and violation of mechanisms of neutralization of ammonia, high levels of which can be forecast-significant criteria in assessment of the severity of the disease. In all cases, PC was accompanied by higher concentrations in blood serum of nitrites, nitrates, S-nitrosothiol in the content comparing with the group of patients with CP ($p < 0.05$).

The special feature of CP and PC was a significant increasing of S-nitrosothiol at complicated forms, which were accompanied by jaundice (Table 3). Thus, at CP the content of S-nitrosothiol in the blood serum of the first subgroup without jaundice was first 0.32 ± 0.03 mmol/l, whereas at patients with jaundice this index rose to 0.80 ± 0.07 mmol/l (the group of conditionally-healthy patients 0.23±0.02 mmol/l). Analogical dynamics of S-nitrosothiol growth in blood serum was observed in patients with PC. These results indicate that S-nitrosothiol may be a forecast indicator of complications development such as jaundice, at CP or PC. Analysis of dynamic index of inducible No-synthase showed that increasing of enzyme activity at CP and its significant reduction in PC which can act as an important criterion in the differential diagnosis of these diseases.

At the same time, the average level of the VEGF blood serum, as a marker of endothelial damage was higher on 26.3% at patients with CP, which was complicated by obstructive jaundice than at patients without jaundice ($r<0.05$). Such tendency was observed

in patients with PC (respectively on 102%, $r<0.05$) and at these patients the average level of VEGF in blood serum was significantly higher than at patients with CP (Table 3).

Our studies indicate that CP and PC combined with the development of endothelial dysfunction, which is revealed by accumulation of toxic metabolic products NO_2, NO_3, NH_3 and others that correlate with the severity of the disease course and the presence of obstructive jaundice. We can assume that the forecast-significant index in the differential diagnosis of CP and cancer of the pancreatic head can not only be inducible No-synthase, but the levels of S-nitrosothiol and blood serum VEGF levels. As the studies have shown that the most informative index for differential diagnosis (CP – PC) is VEGF. The comparison of the average indexes in the groups of patients with CP and PC found threshold valuation of VEGF, which amounted in average of 346 pg/ml, which allowed the separation of these two groups of patients and perform the differential diagnosis. To assess the adequacy of the proposed model was used the value of the area under the ROC-curve (AUC – Area under the ROC curve) with the consideration of 95% confidence interval. The model was considered adequate if the AUC statistically significantly higher than the value of 0.5. At the same time the optimum level (threshold) of the index of forecasting model was chosen based on the ratio of sensitivity and specificity.

During the determination of sensitivity and specificity of the prediction model on the of based VEGF index of endothelial dysfunction in 132 patients (cancer of the head of pancreas – 68, CP with prevalent affection of head of pancreas – 64) area under the ROC-curve (AUC) was 0.764 (0,95 CI 0.683-0.845). The threshold of VEGF, which in average was 346 pg/ml, and divided the groups of patients, was determined on the basis of the criterion of Pareto and sensitivity of this model was 72.1% and specificity of 75% with a total accuracy of 72.7% (Fig. 3).

Even more threshold accuracy of VEGF index, which in average is 248 pg/ ml, during comparing of groups of PC patients and conditionally-healthy people (area under the ROC-curve (AUC) was 0.943 (0.95 CI 0.892-0.994): sensitivity was 86.8% and specificity – 82.4%, the overall accuracy – 82.3% (Fig. 4).

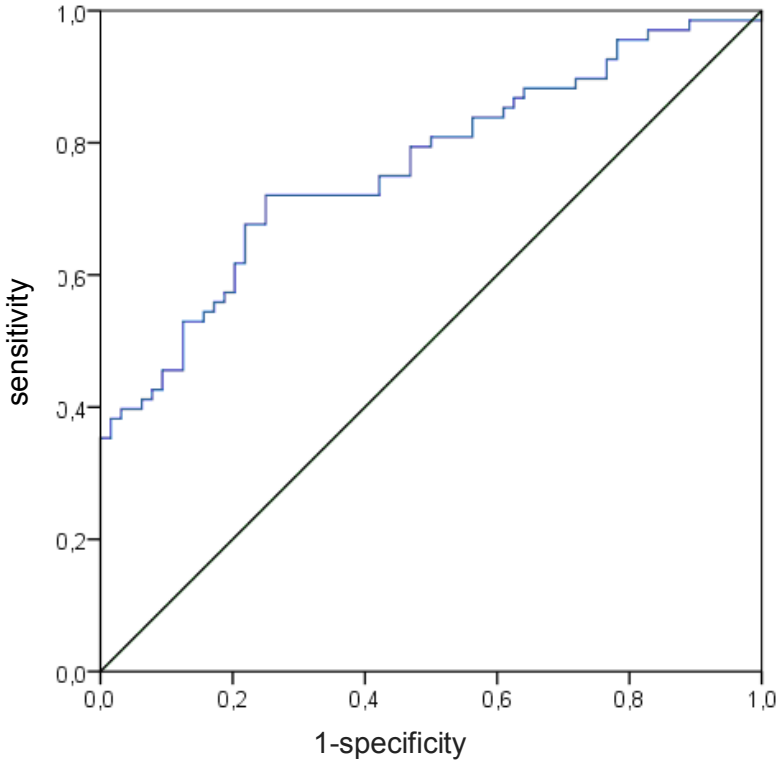

Fig. 3. ROC-curve for patients with CP and cancer of pancreas:

AUC = 0.764 (0.95 CI 0.683-0.845).

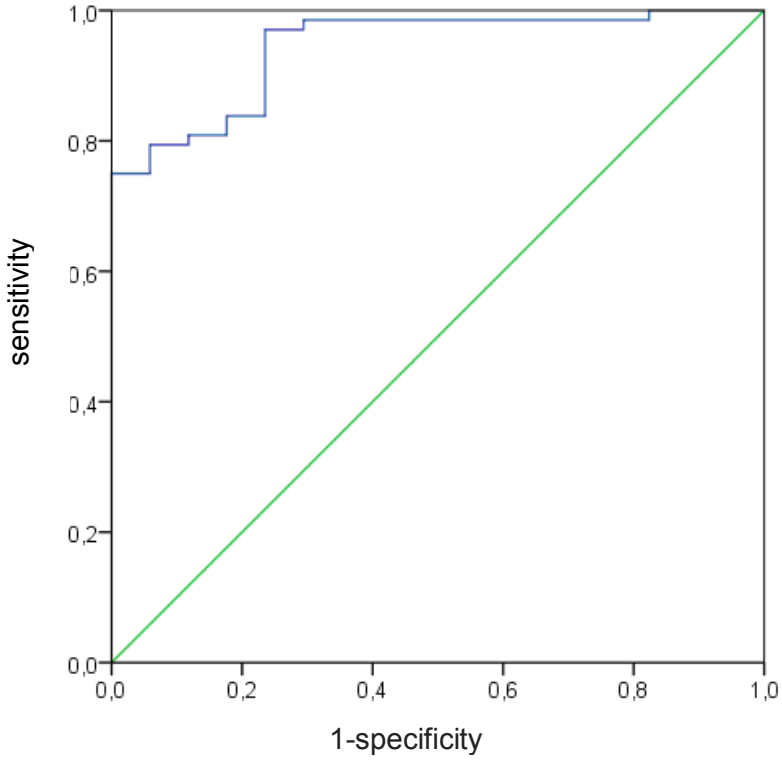

Fig. 4. ROC-curve for patients with pancreatic cancer and a control group:

AUC = 0.943 (0.95 CI 0.892-0.994)

Almost the same accuracy has this criterion and during comparison with the group of CP patients and conditionally-healthy people, the sensitivity was 84.4%, specificity – 76.5%, the overall accuracy – 81.5% at the average threshold of VEGF 155 pg/ml (the area under the ROC-curve (AUC) was 0.866 (0.95 CI 0.764-0.968) (Fig. 5).

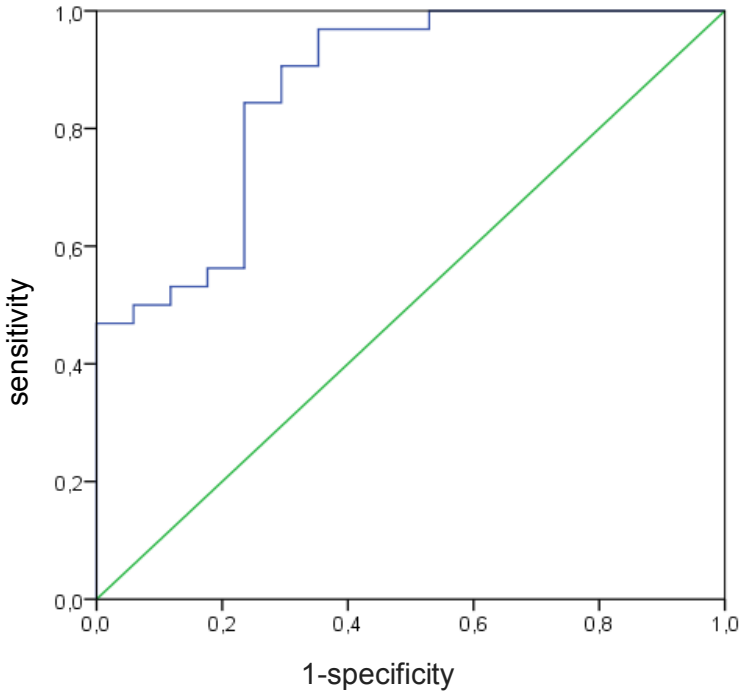

Fig. 5. ROC-curve for patients with CP and a control group:
AUC = 0,866 (0,95 CI 0,764-0,968).

On the next step for the forecasting developing of the basic pathological process, along with the using of diagnostic data, the method of classification tree was also used (Fig. 6). A priori probability of accessories observation of groups were evaluated in a study sample (n=78).

The tree branch contains from three nodes of branching and four terminal tops. Classification accuracy was 89%, the value of cross-checking – 82.6%, which can be supposed as good quality of the model. As it results from given model of the classification tree, the VEGF index at first discriminates patients by the criterion chronic pancreatitis - pancreas cancer and the differences of patients with jaundice is determined by S-nitrosothiol.

Treatment of patients, which was analyzed, had a complex character. If the distal block of biliary tract and chronic jaundice were presented, only ultrasound scanning, MSCT, MR-image and ERC were made.

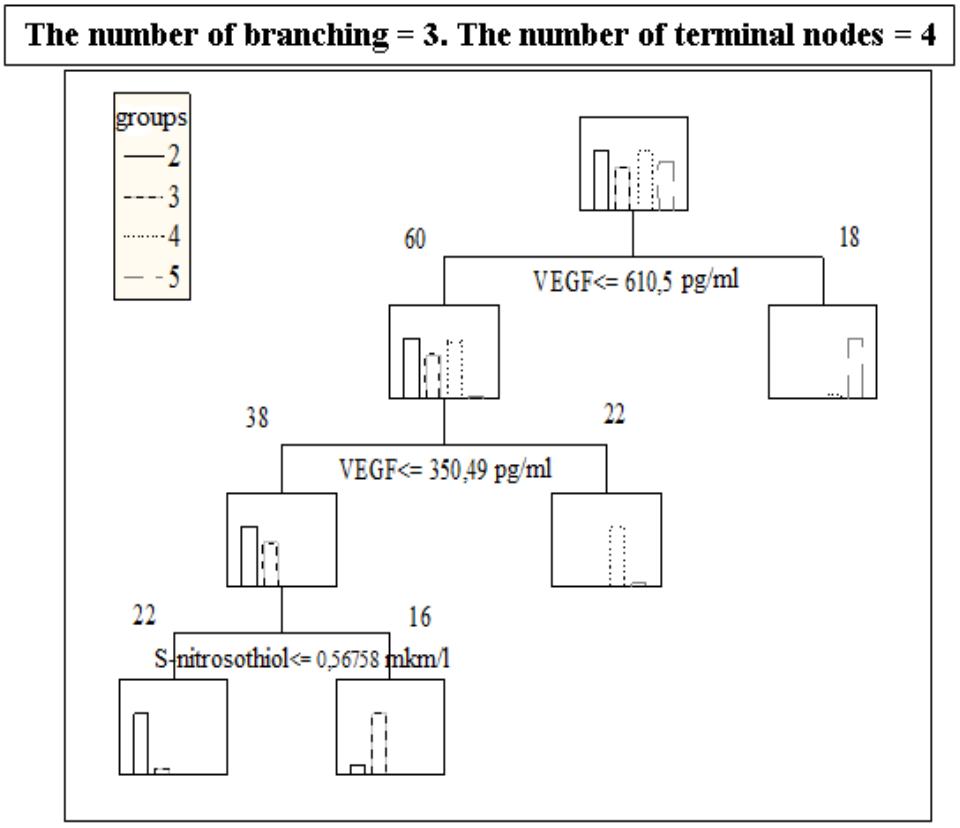

Fig. 6. The classification tree of groups for the differential diagnosis of patients

The reasonability of using every preoperative decompression at obstructive jaundice was detected by the main factors: the level of total bilirubin and its fractions, condition of the patient, informativeness of diagnostic methods, the possibility of transforming the diagnostic procedures to the effective therapeutic intervention, method's safety (probability of complications and the level of their weight) and its technical complexity. Taking into account our experience, we recommend you to follow the next scheme of treatment and diagnostic low-invasive instrumental interventions at CP and PC prevalent affection of the head: clinical and laboratory data, ultrasound (with /without cholecystotomy) MSCT, ERC (with /without EPST and stantation of the bile duct), laparoscopy or laparotomy (with cholecystotomy). If the possibility of low-invasive methods of the decompression of the bile ducts have been exhausted or limited, so after preoperative patient's preparation were made laparotomy with the execution of one of the methods of intraoperative cholepoiesis.

Methods of bile ducts' drainage for temporary or residual bile were performed at 39 of 62 patients with obstructive jaundice (Table 4). At 62 patients with obstructive jaundice 39 (62.9%) were performed decompression surgery after previous biliary system, and in 23

(37.1%) of acute jaundice (10 days) and total bilirubin not more than 150 mkmol/l without jaundice.

Table 4

Methods bile drainage at patients with obstructive jaundice of benign and malignant genesis

Methods of bile ducts' drainage	Amount of patients, av. (%)
ERC, EPST, stantation of bile duct	21 (53,9%)
Cholecystotomy under the of control US	3 (7,7%)
Cholecystotomy under the of control videolaporoscopy	10 (25,6%)
Cholecystotomy with laparotomy mini-access	5 (12,8%)
Total:	39 (100%)

From 132 patients who were operated, pancreatoduodenal resection by Whipple was performed 23, pancreatoduodenal resection by Traverso-Longmire – 8, subtotal right-sided pancreaticstomy by Fortner – 3, hepaticojejunostomy by Roux – 8, duodenal saving resection by Beger – 6, its Berne version – 7, operation by Frey – 51. At the other 26 (19,7%) patients low-invasive interventions to bile's drainage residual interventions through the basic pathological process and heavy general condition of patients. Postoperative complications occurred in 18 (13.6%) patients, died 3 (2.3%).

Conclusion

1. Constructed mathematical models of differential diagnosis and prognosis allow with the high accuracy detect cancer in the presence of the volumetric formation on the head of pancreas. Along with the using of clinical laboratory and instrumental data to decide the issues of the head's pancreas cancer and chronic pancreatitis diagnostic can be used the proposed method for constructing the classification trees, whose accuracy was 89%, the price of cross-checking – 82.6%, which can be considered as good indexes of the model .

2. Low-invasive endoscopic, percutaneous (under the control of US), and videolaporoscopic and lapaparotomy (with mini-access) interference decompression is an effective way for bile drainage restore at obstruction of the biliary system on the background of head's pancreas cancer and chronic pancreatitis. These techniques allow very quickly and effectively eliminate mechanical jaundice and cholangitis and make it possible to carry out surgery in the most favorable conditions, especially at chronic jaundice, routinely, and in patients of elderly age and is the severe concomitant pathology with the alternative of surgical treatment.

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