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ORIGINAL ARTICLE

ERCP combined with tumor markers in differential diagnosis of pancreatic cancer and pseudotumor-like pancreatitis

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Summary

Purpose: *To investigate the significance of endoscopic retrograde cholangiopancreatography (ERCP) combined with tumor markers in the differential diagnosis of pancreatic cancer (PC) and pseudotumor-like pancreatitis (PLP).*

Methods: *A total of 186 patients with PC (pancreatic cancer group) and 89 patients with PLP (pseudotumor-like pancreatitis group) were selected as subjects, and another 268 healthy people during the same period were enrolled as control group. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels of subjects were compared among three groups, these subjects underwent ERCP, and its diagnostic value was analyzed.*

Results: *The levels of serum CEA and CA199 in both PLP and PC group were markedly higher than those in control group and PC group had considerably higher serum CEA and CA19-9 levels in comparison with PLP group ($p<0.05$). The results of area under curve (AUC) showed that ERCP had the highest diagnostic value, CA19-9 had the lowest diagnostic value, and the combined diagnosis had significantly increased accuracy and sensitivity and decreased specificity.*

Conclusion: *The application of ERCP in combination with tumor markers in the differential diagnosis of PC and PLP can evidently improve the diagnostic sensitivity and accuracy, reduce the rate of missed diagnosis of PC, and elevate the survival rate . Therefore, ERCP combined with tumor markers has good application value in clinical practice.*

Key words: *ERCP, tumor markers, pancreatic cancer, pseudotumor-like pancreatitis, differential diagnosis*

Introduction

Pancreatic cancer (PC) is the most common malignant tumor of the digestive system in clinical practice in China. In past two decades, its incidence rate has increased by 6 times in China and 3 times in the United States. In addition, PC ranks 4th in terms of mortality rate among malignant tumors, seriously endangering the life and health of patients [1]. There are no relatively specific diagnostic markers and clinical symptoms at early stage, so the optimal opportunity for treatment is often missed when the disease is detected. Therefore, early diagnosis and treatment of PC is vital to reduce its mortality rate [2].

Currently, the mortality and recurrence rates of PC are gradually elevated due to delayed diagnosis and treatment, making the prognosis and preliminary diagnosis of PC unsatisfactory [3]. A survey showed that less than 30% patients with PC can be diagnosed and treated at AN early stage in clinical practice and the follow-up study on these 30% patients revealed that the 5-year survival rate is increased by about 51% [4]. Hence, the key to diag-

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nose and treat PC is to strengthen the prevention. Meanwhile, high-risk population of PC should be monitored at regular intervals and affected patients should be diagnosed as early as possible. Pseudotumor-like pancreatitis (PLP) is a chronic recurrent pancreatitis with a relatively low incidence rate. At present, it is difficult to distinguish it from PC based on relevant imaging methods and intraoperative findings [5]. As FOR the diagnosis of PC, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are the most commonly-used tumor markers. Moreover, a study manifested that endoscopic retrograde cholangiopancreatography (ERCP) combined with CEA and CA19-9 haD certain value for the diagnosis of PC PLP [6].

The primary purpose of this study was to investigate the significance of ERCP combined with tumor markers in the differential diagnosis of PC and PLP.

Methods

General data

A total of 186 patients with PC (pancreatic cancer group) and 89 patients with PLP (pseudotumor-like pancreatitis group), who were admitted to and treated in hospital from February 2014 to February 2018, were selected as subjects. Another 268 healthy individuals in the same period were enrolled as control group. In PC group, there were 122 males and 64 females aged 30-65 years , with a mean age 42.35±3.62 years. In PLP group, there were 58 males and 31 females aged 30-64 years , with an average age 42.41±3.70 years . In control group, there were 174 males and 94 females 31-65 years old, with a mean age of 42.52±3.71 years . The general data of subjects (including age and gender) showed no significant differences among three groups and were comparable ($p>0.05$). This study was approved by the ethics committee of the Affiliated Hospital of Southwest Medical University. Signed informed consents were obtained from all participants before study entry.

Diagnostic criteria for pancreatic cancer

(1) There was at least one imaging evidence, physical mass or surgical exploration; (2) It was confirmed via pathological diagnosis; (3) There was more than 2 imaging diagnostic supports and any of the following items; a) Space-occupying lesions, dilatation, and stenosis of bile duct or pancreatic duct and the pancreas were detected based on the results of magnetic resonance cholangiopancreatography; b) Common bile duct dilatation and obstruction as well as eccentric stenosis were found according to the findings of percutaneous transhepatic cholangiography; c) Double duct sign, bile duct traction sign, inflexible and irregular duct wall, mouse tail sign of broken end and interrupted pancreatic duct were observed on ERCP results; d) CT results suggested that the pancreas had space-occupying lesions and local enlargement; e) B-mode ultrasonography findings displayed that gallbladder and common bile duct were swollen, pancreatic duct was dilated, and the pancreas had low-density area; f) Positron emission computed tomography examination was performed if necessary; g) Angiography showed that there was vascular invasion outside the pancreas or intrapancreatic tumor blood vessel sign; h) Intraductal ultrasonography manifested that there were space-occupying lesions in the pancreas; and i) Endoscopic ultrasonography showed that the pancreas had low-density space-occupying lesions. People who met any one of the 3 above-mentioned criteria were diagnosed with PC [7]. Patients in the PLP group were definitely diagnosed with via histopathology [8].

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients with PC met the above diagnostic criteria and were accompanied by following symptoms: jaundice, abdominal discomfort, weight loss, dyspepsia, anorexia, and emaciation; 2) Patients in PLP group were definitely diagnosed with via histopathology; 3) This study was approved by the Medical Ethics Committee of the hospital; and 4) Patients and their families agreed and actively cooperated in this study and signed informed consent. Exclusion criteria: 1) Patients complicated with other malignant tumors such as gastric cancer, lung cancer and kidney cancer; 2) Patients with autoimmune disorders; 3) Pregnant or lactating women; or 4) Poor compliance or patient withdrawal.

Methods

All subjects underwent ERCP.

1) Determination of serum CA19-9 and CEA levels: Fasting venous blood (5 mL) was collected from all subjects in early morning, added with 35 uL 10% ethylenediaminetetraacetic acid for anticoagulation, and centrifuged at 4°C, 3000 r/min with a centrifugal radius of 10.5 cm for 10 min using a centrifuge [Ortho BioVue, Johnson & Johnson (Shanghai, China) Medical Equipment Co., Ltd.]. Next, the serum was collected and stored in a refrigerator at -75°C for subsequent testing. Then, the serum CA19-9 level was measured using a chemiluminescence immunoassay system (Dxl800 Access, Beckman, Miami, FL, USA), and the kit was purchased from Roche. The serum CEA level was determined through enzyme-linked immunosorbent assay, and the kit was purchased from Elsbio, Suzhou. The range of critical values were defined as follows: CEA <5 ng/mL and CA19-9 <37 U/Ml, negative, CA19-9 ≥37 U/Ml and CEA ≥5 ng/mL, positive [9]. Criteria for a positive ERCP: 1- Filling defects in pancreatic duct, 2- rough and irregular acinar shadows and contrast agent retention in pancreas, 3- Displacement, interruption, and stenosis in main pancreatic duct , 4- Displacement in pancreatic branch duct, and 5- Double duct sign [10].

2) Result judgement: The accuracy, specificity, and sensitivity of the diagnosis of PC were calculated according to the serum tumor markers for each group of subjects [11]. Accuracy = number of negative cases in healthy control group + number of positive cases in PC group / number of all cases in healthy control group + number of all cases in PC group ×100%; Specificity = number of

negative cases in control group / number of all cases in control group ×100%; Sensitivity = number of positive cases in PC group / number of all cases in PC group ×100%.

Statistics

SPSS 20.00 software (IBM, Armonk, NY, USA) was used to analyze the data. Measurement data was expressed as (x±s), t-test was employed for two sets of data, and F test was adopted for multiple sets of data. Enumeration data were expressed as [n (%)] and subjected to x^2 test. Receiver operating characteristic (ROC) curve was applied to analyze the efficiency of CA19-9, CEA, and ERCP (used as single or combined) and determine their critical values. P value <0.05 suggested diagnostic significance.

Results

Comparisons of serum CEA and CA19-9 levels among three groups

The differences in the serum CEA and CA19-9 levels were statistically significant among three groups (p<0.05). The levels of serum CEA and CA19-9 in PLP group and PC group were significantly higher than those in control group and PC group had overtly elevated serum CEA and CA19-9 levels in comparison with PLP group (p<0.05) (Table 1).

Results of serum CEA, CA19-9, the predictive probability pre-1, and ERCP in pancreatic cancer group

With the result of diagnosis as a state variable and CEA, ERCP, CA19-9 and the predictive probability pre-1 as the test variables, the ROC curve was plotted (Figure 1). In addition, the results of AUC showed that ERCP had the highest diagnostic value, whereas CA19-9 had the lowest diagnostic value (Table 2 and Figure 1).

Results of serum CEA, CA19-9, the predictive probability pre-1, and ERCP in pseudotumor-like pancreatitis group

Considering the result of diagnosis as a stable variable and CEA, ERCP, CA19-9 and the predic-

Table 1. Comparisons of serum CEA and CA19-9 levels among three groups

Groups	*CEA (ng/mL) mean±SD*	*CA19-9 (U/mL) mean±SD*
Control group (n=268)	3.32±1.25	54.35±16.63
Pseudotumor-like pancreatitis group (n=89)	8.72±3.66*	100.57±17.25*
Pancreatic cancer group (n=186)	11.98±5.02#	253.18±20.31#
F	10.964	19.865
P	<0.001	<0.001

Compared with control group, *p<0.05. Compared with pancreatitis group, #p<0.05

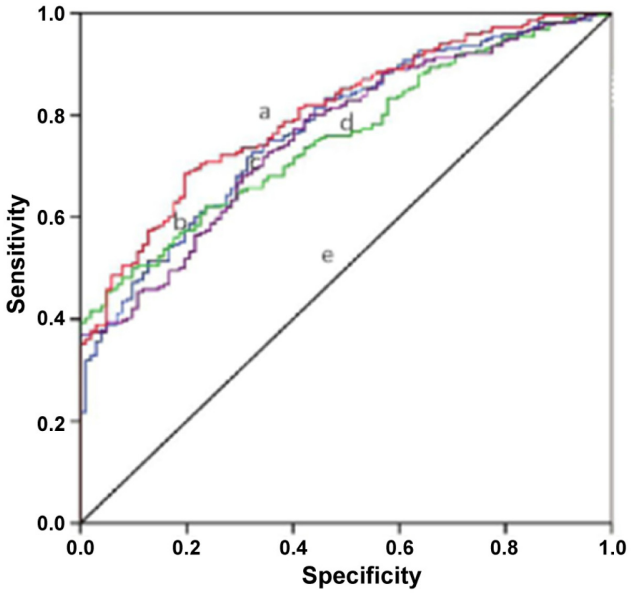

Figure 1. ROC curves of serum CEA, CA19-9, the predictive probability pre-1, and ERCP in pancreatic cancer group. **a:** pre-1, **b:** ERCP, **c:** CEA, **d:** CA199, **e:** Reference line. .

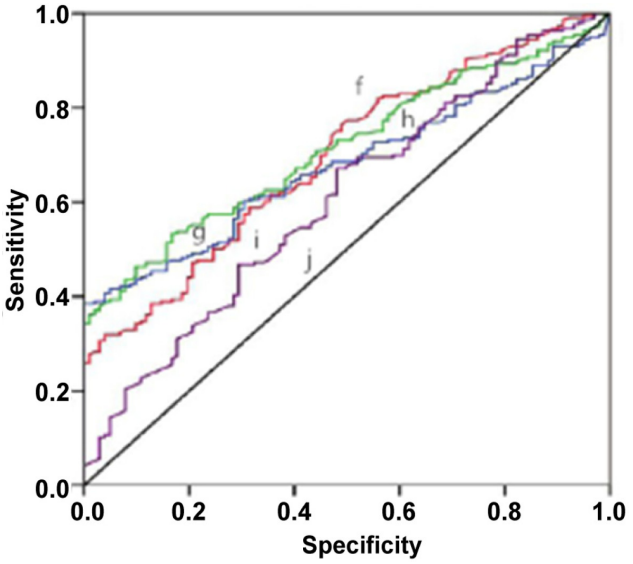

Figure 2. ROC curves of serum CEA, CA19-9, the predictive probability pre-1, and ERCP in pseudotumor-like pancreatitis group. **f:** pre-1, **g:** ERCP, **h:** CEA, **i:** CA199, **j:** Reference line.

Table 2. Results of patient serum CEA, CA19-9, the predictive probability pre-1, and ERCP in pancreatic cancer group

	AUC	*95% confidence interval*	*Standard error*	*p*
ERCP	0.876	0.779-0.836	0.030	0.000
CEA	0.854	0.726-0.871	0.031	0.000
CA19-9	0.723	0.645-0.814	0.025	0.001
Pre-1	0.945	0.925-0.985	0.017	0.000

Table 3. Results of serum CEA, CA19-9, the predictive probability pre-1, and ERCP in pseudotumor-like pancreatitis group

	AUC	*95% confidence interval*	*Standard error*	*p*
ERCP	0.739	0.701-0.829	0.028	0.000
CEA	0.702	0.635-0.796	0.033	0.000
CA19-9	0.669	0.621-0.782	0.026	0.000
Pre-1	0.832	0.806-0.897	0.019	0.000

Table 4. Analysis of results of serum tumor markers and ERCP (alone and combined diagnoses) in pancreatic cancer

	ERCP %	*CA19-9* %	*CEA* %	*ERCP +CEA +CA19-9* %
Sensitivity	85.48	76.88	69.35	95.16
Specificity	93.26	95.03	96.72	90.89
Accuracy	89.13	86.19	80.61	92.27
Positive predictive value	91.34	93.52	95.12	60.35
Negative predictive value	87.36	81.46	77.38	93.26

Table 5. Analyses of results of serum tumor markers and ERCP (alone and combined diagnoses) in pseudotumor-like pancreatitis

	ERCP %	*CA19-9* %	*CEA* %	*ERCP +CEA +CA19-9* %
Sensitivity	81.32	65.39	61.09	91.35
Specificity	92.17	94.20	95.36	89.32
Accuracy	85.96	83.25	76.32	89.36
Positive predictive value	90.69	92.64	94.63	62.37
Negative predictive value	78.63	76.32	75.65	87.39

tive probability pre-1 as the test variables, the ROC curve was plotted (Figure 2). The results of AUC showed that ERCP had the highest diagnostic value, while CA19-9 had the lowest diagnostic value (Table 3 and Figure 2).

Analyses of results of serum tumor markers and ERCP (alone and combined diagnoses) in pancreatic cancer

For diagnosis of PC using single method, ERCP had the highest sensitivity (85.48%), and CEA had the highest specificity (96.72%). As for the diagnosis using the combination of ERCP and tumor markers, its accuracy was increased to 92.27%, its sensitivity was elevated to 95.16%, but its specificity was declined slightly (Table 4).

Analyses of results of serum tumor markers and ERCP (alone and combined diagnoses) in pseudotumor-like pancreatitis

For diagnosis of PLP using single method, ERCP had the highest sensitivity (81.32%) and CEA had the highest specificity (96.72%). As for the diagnosis through the combination of ERCP and tumor markers, its accuracy was enhanced to 89.36%, its sensitivity was raised to 91.35%, but its specificity was decreased slightly (Table 5).

Discussion

Tumor markers are referred to as substances abnormally increased or produced due to response of the body to tumors or secreted because of direct gene expressions of tumor cells during proliferation or the onset of diseases, which can reflect the growth and existence of tumors to some extent and have certain value for prognosis, efficacy of treatment evaluation, and clinical diagnosis [12]. Clinically, there are certain limitations for ideal tumor markers: They should have good predictable and evaluable value for prognosis and treatment effect, have good correlations with the tumor stage, size and aggressiveness and locate tumor high specificity and sensitivity.

PC, like other tumors, occurs gradually through multiple complex biological processes and relatively long periods of time. As a result, it is difficult to accurately diagnose PC, especially in early stage, and it is not currently possible to diagnose it using a specific and sensitive method [13]. Chronic pancreatitis is a chronic progressive and irreversible disease of the pancreas. Clinically, it is hard to diagnose and the main and definite diagnosis is made by histopathology of the pancreatic mass. However, obtaining pancreatic tissue specimens from an alive individual is a therapeutic challenge when performed by puncture, resulting in limited outcomes in the diagnosis of pancreatitis due to the effects of puncture level and pancreatic fistula complications [14]. Therefore, in clinical practice, pancreatitis is usually diagnosed based on typical imaging findings, pancreatic exocrine function, pancreatic enzyme activity, and clinical manifestations at initial presentation.

PLP, a type of chronic pancreatitis, is characterized by absence of a focal non-calcified mass in the pancreas, which is very similar to tumors, making its differential diagnosis from PC extremely difficult [15].

CA19-9 is a glycoprotein located on the cell membrane and expressed in the pancreatic ductal epithelium of normal healthy people, which is usually present in the serum in the form of sialomucin. The content of serum CA19-9 is relatively low in healthy people. When the ductal epithelial cells of the body become cancerous, the gene that regulates mucin is activated by external stimulation, up-regulating the expression of CA19-9 [16]. In addition, pancreatic duct and small pancreatic duct are blocked by tumor cells, leading to increased accumulation of CA19-9 and gradual transfer to the blood and matrix around neoplastic foci, and ultimately resulting in gradually risen serum CA19-9 level [17]. Moreover, clinical studies have shown that serum CA19-9 level is usually affected by many factors and there are different levels of CA19-9 in endometrium, breast, stomach, gallbladder, bile duct, and pancreas. When some tumors occur in the above-mentioned tissues and organs, the content of CA19-9 in the serum will be elevated, easily giving rise to false-positive diagnosis. Therefore, the value of CA19-9 alone in the diagnosis of PC is low.

CEA, separated from embryonic colon and colon cancer mucosa tissues by Gold in 1965, is a member of the glycoprotein family located on the cell surface, which is mainly used for the auxiliary diagnosis of common gastrointestinal tumors such as colon cancer and PC [18]. Hence, tumor markers have certain value for the diagnosis of PC and PLP.

In ERCP a contrast agent is injected through duodenal papilla intubation with the aid of an endoscope in order to retrogradely display the pancreaticobiliary duct, which is able to clearly reveal the lesions of the main pancreatic duct and the pancreatic branch duct [19]. However, lymph node and vascular invasion cannot be observed via ERCP and ERCP has certain difficulties in the diagnosis of smaller tumors at the tail of the pancreas or tumors that do not invade the pancreatic duct. Therefore, the accuracy and sensitivity of ERCP alone is relatively low in the diagnosis of PC and PLP [20]. The ROC curve of the combination of the above-mentioned tumor markers and ERCP in the diagnosis of PL and PLP showed that the accuracy and sensitivity were significantly increased, while the specificity was decreased to a certain extent, implying that the diagnosis using the combination of methods has raised the accuracy and sensitivity at the expense of specificity and can better differentiate PC from PLP, so that targeted treatment can be given as early as possible in order to improve the survival rate of patients.

In conclusion, for the diagnosis of PC and PLP, ERCP combined with tumor markers can evidently increase the diagnostic sensitivity and accuracy, lower the rate of missed diagnosis, and indirectly improve the survival rate of patients.

Conflict of interests

The authors declare no conflict of interests.

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