Application of biochemical markers CA 19-9, CEA and C-reactive protein in diagnosis of malicious and benign pancreatic tumors

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Abstract

Introduction: We would save many lives and spare a lot of suffering if we could only detect and accurately determine the character and TMN staging of pancreatic tumors (PTs). With improved diagnosis, we could offer specific treatment that would result in better treatment outcome. The aim of study was to determine the significance of neoplastic markers CA 19-9 and CEA for prognosis in inflammatory and carcinomatous PTs.

Material and methods: We based our research upon a group of 170 patients. The patients were treated in our Oncologic Surgery Department from January 2007 to December 2010 for PTs. The patients were divided into four groups depending on the character of the tumor and underwent the following treatments: group 1 – 34 patients with carcinoma of the ampulla of Vater, group 2 – 64 patients with PTs at different stages (1, 2, 3) according to TMN classification, group 3 – 62 patients with PTs at stage 4 on the TMN scale (unresectable tumors), group 4 – 28 patients with inflammatory PTs.

Results: The results of Ca 19-9 in group 2 were 736.00 (25–75% 220.40–4285.00) ng/ml before surgery, 53.00 (25–75% 12.60–84.00) ng/ml in the 7 days after surgery, 29.4 (25–75% 7.90–113.00) ng/ml at day 30, and 119.00 (25–75% 96.30–621.00) ng/ml 3 months after the operation. These results were significantly higher than the control group but were significantly lower than the results for group 3 (unresectable tumors). The highest average concentration and median for CA 19-9 and CEA were noted in patients with unresectable PTs (the 3rd group). The average concentration for CEA was lowest in group 4, but much higher than the lab limits.

Conclusions: The sensitivity of the CA 19-9 marker may be as high as 88%. Values of CA 19-9 above 852 U/ml may indicate TNM stage 4, consistent with an unresectable PT. In the cases where CA 19-9 is within normal limits but C-reactive protein is above normal limits (often thirty times the upper limit), in comparison to the control group and to patients with pancreatic neoplasms, strong consideration should be given towards the inflammatory characteristics of the pancreatic changes and conservative treatment should be applied.

Key words: CA 19-9, CEA, pancreatic tumors.

Introduction

Difficulties in detecting and determining the character of pancreatic tumors (PTs) often result in poor treatment and outcome. Our goal is to detect PTs in a timely manner before they encroach upon biliary tracts or metastasize. In these scenarios we can only offer palliative surgery to relieve pain and overwhelming icterus [1].

It is hard to believe that despite the vast array of diagnostic tools we have at our disposal, a surgeon performing a pancreatic tumor procedure does not know exactly what to expect. Some of the perplexing questions they face are:

- Is the tumor benign or malignant?
- Is the neoplasm resectable or not?
- If the PT turns out to neoplastic, what is its tumor metastasis node (TMN) staging?

It goes without saying that different tumors require different surgical and anesthesiological (central line, TEA) approaches, but the final decision as to the extent of the surgery is made intraoperatively, often complicating the matter even further. Last, but not least, is the fact that we often add pain to misery if during explorative laparotomy we abandon the operation due to the unresectable nature of the tumor (TMN 4).

Data from the USA indicate that the incidence of pancreatic cancers is 8 to 12 per 100 000 people per year. In total, there are about 32 000 cases of this disease annually in the USA. Pancreatic cancer is the fourth leading cause of mortality from neoplastic disease in the USA, despite constituting only 3% of all cancers [2].

The epidemiology of pancreatic tumors is similar in Poland. There are roughly 3 500 cases every year and they constitute 2.5% of all carcinomas. On average, upon resection the patient's life expectancy is around 24 months and it is shortened to 11 weeks in cases where palliative procedures alone are carried out [3–5].

Table I. Clinical use of tumor markers

No.	Tumor type	Tumor marker
1	Pancreatic cancer	Ca 19-9
2	Colorectal cancer	CEA, Ca 19-9
3	Breast cancer	Ca 15-3
4	Cervical cancer	SCC-Ag
5	Prostate cancer	PSA, PAP
6	Hepatocellular cancer	AFP
7	Gastric cancer	Ca 19-9, CEA
8	Lung cancer	NSE, SCC-Ag, Cyfra 21-1, CEA
9	Testis tumor	Beta HCG, AFP, PLAP
10	Ovarian tumor	Ca-125, β-HCG, AFP, CEA
11	Thyroid cancer	Thyroglobulin, calcitonin

Signs and symptoms of PTs are few and far between and often only manifest when it is too late for intervention. The main symptoms are icterus (82%), GI discomfort (32%), anorexia and weight loss (29%), pruritus (21%), nausea and vomiting or diarrhea often leading to cachexia and death. Often the very first sign of the illness is upper gastrointestinal bleeding. Even after diagnostic procedures such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound, there is still a lack of certainty of definitive diagnosis with PTs. Every patient should be approached as an oncological case until proven otherwise [6–8].

The above-mentioned signs and symptoms of PTs are usually late and nonspecific and, therefore, the positive long-term treatment results for this illness are poor. Efforts are underway to find sensitive and specific lab biomarkers for PTs, allowing for prediction of the character of the tumor. When these biomarkers are found, we will be able to tell in advance whether the PT is resectable and the type of surgical procedure that will offer the best results. Unfortunately, we can only determine the character of the PT upon histological examination of the removed tumor mass, which is usually too late. Upon laparotomy we often find that the PT is unresectable and we resort to a palliative procedure restoring efflux of bile and sympathectomy for pain relief. The main difference between procedures now versus those in the eighties is the application of laparoscopic removal of PTs instead of open laparotomy [9].

It should also be noted that the two primary goals of palliative treatment are often accomplished by different methods, namely by endoscopic retrograde cholangiopancreatography (ERCP) (bile efflux) and video-assisted thoracoscopic sympathectomy (VATS) (sympathectomy) [10].

Although a number of lab biomarkers have already been tested as predictors of PTs, few are of any importance (Table I). Our main objective was to determine whether the concentration of the neoplastic markers carcinoma antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) can distinguish PTs versus inflammatory changes in the pancreas.

Material and methods

From January 2007 to December 2010 (4-year period), we enrolled 170 patients who were diagnosed with PTs which included benign, malignant, and inflammatory tumors. All of these patients underwent routine bedside examinations (physical, labs) and went through a series of abdominal cavity examinations as well as USG, ERCP, magnetic resonance cholangiopancreatography (MRCP) and/or MRI.

Upon finishing treatment, we divided the patients into four groups based upon lab tests and

histopathological results (done only upon removal of PTs):

- group 1 – 34 patients with carcinoma of the ampulla of Vater,
- group 2 – 64 patients with PTs at different stages (1, 2, 3) according to TMN classification,
- group 3 – 62 patients with PTs at stage 4 on the TMN scale (unresectable tumors),
- group 4 – 28 patients with inflammatory PTs.

In group 3 the following treatments were performed: surgical bypass with anastomosis, including gastrojejunostomy or mixed gastrojejuno- and cholecysto-jejunostomy (triple bypass).

Blood samples (2 ml) were taken through the antecubital vein on the day of the operation and then at 7, 30 and 90 days after the operation in all groups and the levels of CEA and CA 19-9 were determined. The blood was centrifuged and stored at –60°C. Levels of CEA, CA 19-9 and CRP were determined by standard electrochemiluminescence assay (ECLIA), method by means of Roche (CEA Kit No. 11731629322, CA19-9 Kit No. 11776193122, CRP Kit No. 11761428622). The study was performed using a Cobas 601 device. The patients were fasting at the time of sampling.

The fifth group was a control group composed of 20 patients who suffered from asymptomatic gallstones and were scheduled to have a cholecystectomy. The presence of any neoplastic disease in these patients was excluded. The blood samples were taken in this group in the same manner as described above.

Patients with active endocrine tumors of the gastroenteropancreatic neuroendocrine tumor (GEP-NET) type were also excluded from the research.

We were only able to follow up 57% of the initially enrolled patient population. Their medical records were scrutinized thoroughly. The remaining patients either did not report to the clinic or their family and friends refused to share any relevant information about them.

All patients signed informed consent and ethical committee approval no. RNN/592/11/KB was obtained.

Statistical analysis

Statistical analysis was carried out with the help of Statistica 9.5. ANOVA and post hoc tests were used to check that results in all five groups were correct and had statistical significance. The statistical differences between values of CA 19-9 and CEA were checked periodically (see above) and compared with Freidman's ANOVA test. The results were also scrutinized based on ROC (receiver operating characteristic) curves showing linear interdependencies between sensitivity and specificity for each of the markers (CEA and CA 19-9). A median was applied to compare results given scattering of the data and count of the groups.

Results

After analysis, the level of the highest median of CA 19-9 recorded in group 3 was 4578.00 (25–75% 1456.00–9600.00) ng/ml before surgery, 4,761.00 (25–75% 1680.00–10,560) ng/ml in the 7 days after surgery, 5730.00 (25–75% 2300.00–11805.00) ng/ml at day 30, and 9600.00 (25–75% 4765.00–14200.00) ng/ml 3 months after surgery. The results from group 3 were significantly different than those from the control group and the other groups (Tables II and III).

From a clinical point of view, the greatest practical value is in the results of CA 19-9 in group 2. The levels from group 2 were 736.00 (25–75% 220.40–4285.00) ng/ml before surgery, 53.00 (25–75% 12.60–84.00) ng/ml in the 7 days after surgery, 29.4 (25–75% 7.90–113.00) ng/ml at day 30, and 119.00 (25–75% 96.30–621.00) ng/ml 3 months after the operation. These results were significantly higher than those in control group 4 and significantly lower than in group 3. There were no statistically significant differences in comparison with group 1. The level of the highest median of CRP was recorded in group 4 (Table IV). The summary of CEA median results is shown in Table V. The results from group 3 were significantly different than those from the control group and the other groups. The sensitivity of CEA was 0.462 and specificity 0.7 (AUC= 0.727); however, sensi-

Table II. Median concentration of CA 19-9 in the studied groups of patients

Before surgery	CA 19-9					
	Median	25–75%	*p**	*p***	*p****	*p*****
Carcinoma of the Ampulla of Vater	55.150	16.50–110.30				
PTs at different stages (1, 2, 3)	736.000	220.40–4285.00				0.0022
PTs at stage 4	4578.000	1456.00–9600.00	0.0087		< 0.001	< 0.001
Inflammatory PTs	24.700	8.80–61.80		0.027		
Control group	13.30	6.30–16.00				

**Comparison with carcinoma of the ampulla of Vater, **comparison with PTs at different stages (1, 2, 3), ***comparison with inflammatory PTs, ****comparison with control group*

Table III. Median concentrations of CA 19-9 in 90 days of study

90 days	CA 19-9					
	Median	25–75%	*p**	*p***	*p****	*p*****
Carcinoma of the ampulla of Vater	29.10	12.60–63.50				
PTs at different stages (1, 2, 3)	119.00	96.30–621.00				
PTs at stage 4	9600.00	4765.00–14200.00	< 0.001	0.0483	< 0.001	< 0.001
Inflammatory PTs	27.15	7.50–63.54				
Control group	13.30	6.30–16.00		0.0311		

**Comparison with carcinoma of the ampulla of Vater, **comparison with PTs at different stages (1, 2, 3), ***comparison with inflammatory PTs, ****comparison with control group*

Table IV. Median CRP levels before the surgery

Before surgery	CRP					
	Median	25–75%	*p**	*p***	*p****	*p*****
Carcinoma of the ampulla of Vater	70.00	23.80–92.00				
PTs at different stages (1, 2, 3)	38.70	11.00–74.00				
PTs at stage 4	48.90	26.70–85.80			0.043	0.0244
Inflammatory PTs	166.40	109.00–267.00		0.0248		
Control group	4.95	3.5–6.1			< 0.001	

**Comparison with carcinoma of the ampulla of Vater, **comparison with PTs at different stages (1, 2, 3), ***comparison with inflammatory PTs, ****comparison with control group*

Table V. Median CEA levels before the surgery

Before surgery	CEA					
	Median	25–75%	*p**	*p***	*p****	*p*****
Carcinoma of the Ampulla of Vater	2.55	1.78–3.50				
PTs at different stages (1, 2, 3)	4.10	2.15–6.04				
PTs at stage 4	13.93	17.76–26.80	< 0.001		< 0.001	< 0.001
Inflammatory PTs	3.25	1.78–4.25				
Control group	2.55	1.70–3.60				

**Comparison with carcinoma of the ampulla of Vater, **comparison with PTs at different stages (1, 2, 3), ***comparison with inflammatory PTs, ****comparison with control group*

tivity of CA 19-9 was 0.889 and specificity 0.9 (AUC = 0.9) (Table V).

Discussion

Today worldwide, up to 30% of operations performed on patients with pancreatic tumors are "unnecessary" [5]. Some represent operations carried out in patients with benign tumors and others are laparotomies in patients with stage 4 malignancy. At present, we have no means by which to distinguish benign from malignant tumors pre-surgically with 100% certainty. Knowing even a single ideal biomarker that can answer the question of whether the patient has pancreatic cancer before surgery would allow for the exclusion of more than 30% of these procedures, which ultimately should not be performed.

Suspicion of a specific cancer would denote a particular level of a corresponding biomarker in order to confirm or exclude the disease (sometimes more than one, to differentiate between tumors), while determination of a panel of markers in every case of suspected malignancy is not advisable [10, 11].

When diagnosing pancreatic cancer, patients must fulfill criteria or risk factors for the disease. Today, a confirmed and well-known risk factor for pancreatic cancer is nicotine and occupational exposure to certain chemicals (benzidine and β-naphthylamine) [12–14]. Currently, the best known and examined pancreatic cancer marker is CA 19-9. The characteristics of an ideal marker are high sensitivity, high specificity, predictive value and specificity of the organ [15].

Specificity is the proportion of patients who are normal or have benign disease, in whom the values obtained in the test are negative (i.e. below the threshold). A lower percentage of false positives results in a higher specificity for the marker. Speci-

ficity tells us about the ability of a test to identify healthy individuals [16].

In contrast, sensitivity is the proportion of patients with cancer, in whom the values obtained in the test are positive. The lower the percentage of false-negative results, the higher the sensitivity of the marker. Sensitivity is the ability of the test to detect disease. CA 19-9 has been shown to have a specificity of approximately 85% and a sensitivity of 90% [15, 17]. In our study, the sensitivity is 88%. Therefore, the search for the perfect marker persists. At present, we know the standards, the specificity and sensitivity of the marker, but we do not know if exceeding the normal range, e.g. 2 or 4-fold, may indicate an unresectable tumor.

The surgeon could allow the possibility to gauge preoperatively whether surgery should be performed and possibly allow distinction between benign tumors of the pancreas and those that are contraindicated for surgical removal. The tumor stage gives the possibility of radical surgery and a potentially good prognosis or disqualifies the patient from surgery and does not expose the patient to operative trauma as well as the possibility of complications.

The prognostic value of CA 19-9 as a marker of survival in pancreatic cancer is higher postoperatively rather than preoperatively [18]. It was also found that level of CA 19-9 is an independent prognostic factor [19]. Reni *et al*. [20] studied a group of patients undergoing neoadjuvant chemotherapy in advanced pancreatic cancer, depending on the level of CA 19-9. Average concentration of CA 19-9 serum levels above 1167 U/ml allows for survival of only 8 months.

CA 19-9 is also used in the differentiation between benign and malignant intraductal papillary mucinous neoplasms. High sensitivity, close to 86%, makes it possible to predict malignant change [21, 22]. But 86% does not give certainty. The question is how to proceed? Despite a lack of diagnosis of malignant changes, should we expose the patient to significant treatment, or watch and wait, allowing the possible progression of cancer?

In all doubtful or controversial cases, those with lack of a diagnosis of malignant change, or in the presence of cysts or cystic glandular changes, UK authors recommend aggressive surgical management [23] with all its ensuing consequences.

After analyzing our results, we found a significantly higher median level of CA 19-9 before surgery in patients with inoperable pancreatic cancer compared to the other groups (average concentration of 6230 U/ml and a median of 4578 U/ml). As the number of days increased (7^{th} day – average median of 4761 U/ml) up to 90 days (average median 9630 U/ml) the average median increased. Such high values at any point are considered strong evidence of the progress of the disease.

However, there were significantly higher median levels of CA 19-9 in patients with operable pancreatic cancer in relation to the control group before treatment (mean concentration of 852 U/ml and a median of 736 U/ml) and these levels decreased in the subsequent postsurgical period with a decrease of 7 to 30 times with no statistical difference. At 3 months after surgical resection, the median CA 19-9 levels were again significantly different compared with the control group. There may be a temporary regression of the resected tumor which could possibly be caused by local recurrence and/or changes in the site of metastasis. The sensitivity and specificity of CA 19-9 in the control group compared to the group of patients with resectable pancreatic cancer in the initial phase of the study was high, reaching 90–92% with a cut-off point of 32 U/ml, with an AUC of 0.9 that respectively decreased over time after surgery between 32–53%,

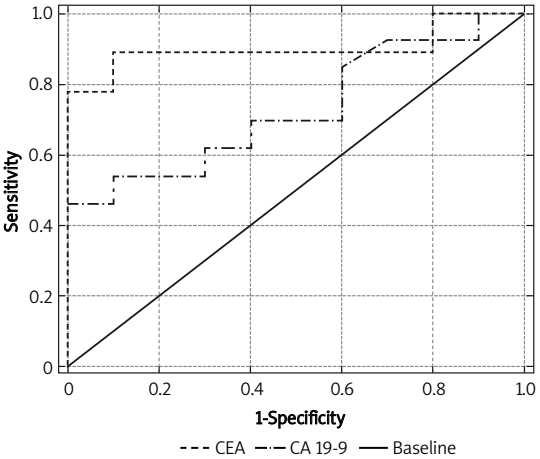

Figure 1. ROC curve for CA 19-9 and CEA before operations in the control group and in patients with operable pancreatic tumor

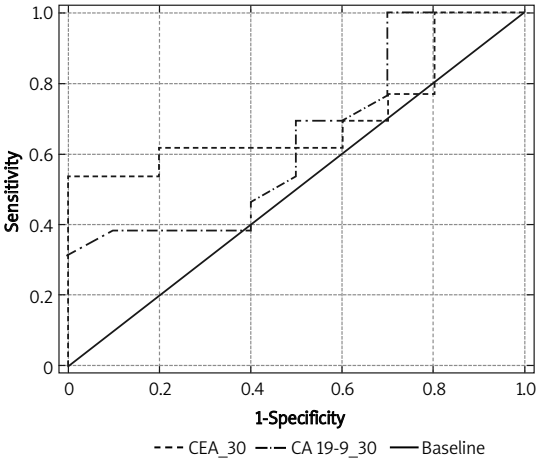

Figure 2. ROC curve for CA 19-9 and CEA after 30 days of testing in the control group and in patients with operable pancreatic tumor

and an AUC of 0.642 for the same cut-off point at day 30 (Figure 2). This may be evidence of the effectiveness of surgical treatment. Histopathological findings were analyzed in 4 cases (9%) which had R1 resection and the remaining R0. We will discuss this topic in a future study.

Interesting observations can be drawn by analyzing the group of patients with nonmalignant pancreatic tumors. Determination of preoperative CA 19-9 and CEA with no statistical differences compared to the control group and significantly higher median concentrations of CRP (normal value exceeded more than 30-fold) may indicate the presence of an inflammatory tumor of the pancreas (Table IV).

A Polish research group [24] looked for an ideal marker using matrix metalloproteinases (MMP), proteolytic enzymes involved in the processes of angiogenesis and collagen fiber structure of the extracellular matrix along with their inhibitors TIMP. It was found that MMP may be an independent predictor of survival in patients with pancreatic cancer.

There is also ongoing research of the carcinoembryonic antigen and its role in pancreatic cancer. Its specificity is low. Pitman *et al*. [25] concluded that the presence of atypical cells in the fluid of a pancreatic cyst has more prognostic significance than the concentration of CEA in the fluid with values greater than 2500 ng/ml. Our study confirms a low clinical utility of this marker in the diagnosis and differential diagnosis of pancreatic neoplasms. CEA values were significantly higher throughout the study period only in patients with unresectable cancer, which may indicate the existence of metastases, e.g. to the liver, during the simultaneous diagnosis of disease in the pancreas.

In conclusion, The highest average and median concentration of CA 19-9 and CEA are present in patients with unresectable pancreatic cancer. Average median CEA concentration was lowest in patients with inflammatory tumors, but significantly higher than that of normal patients. The sensitivity of the marker CA 19-9 in malignant tumors of the pancreas reaches 88%. The average concentration of the marker CA 19-9 above 852 U/ml may be a stage 4 cancer and unresectable pancreatic tumor. In cases where CA 19-9 is within normal limits but CRP is above normal limits (often thirty times over the upper limit) in comparison to the control group and to patients with pancreatic neoplasms, strong consideration should be given to the inflammatory characteristics of the pancreatic changes and conservative treatment should be applied.

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