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TPS, CA 19-9, VEGF-A, and CEA as Diagnostic and Prognostic Factors in Patients with Mass Lesions in the Pancreatic Head

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Abstract

Introduction: Although numerous tumour markers are available for periampullary tumours, including pancreatic cancer, their specificity and sensitivity have been questioned.

Materials and methods: To assess the diagnostic and prognostic values of tissue polypeptide specific antigen (TPS), carbohydrate antigen 19-9 (CA 19-9), vascular endothelial growth factor (VEGF-A), and carcinoembryonic antigen (CEA) we took serum samples in 56 patients with mass lesions in the pancreatic head. Among these patients, further investigations revealed pancreatic cancer in 20 patients, other malignant diseases in 12 and benign conditions in 24.

Results: Median CEA in all patients was 3.4 µg/L (range 0.5–585.0), median CA 19-9 was 105 kU/L (range 0.6–1 300 00), median TPS 123.5 U/L (range 15.0–3350) and median VEGF-A 132.5 ng/L (range 60.0–4317). Area under the curve was 0.747, standard error (standard error [SE] = 0.075) for CEA, 0.716 (SE = 0.078) for CA 19-9 and 0.822 (SE = 0.086) for TPS in ROC plots based on the ability of the tumours to distinguish between benign and malignant conditions. None of the markers significantly predicted survival in the subgroup of patients with pancreatic cancer.

Discussion: Our study shows that the markers may be used as fairly reliable diagnostic tools, but cannot be used to predict survival.

Introduction

Tumours occurring around the papilla of Vater, often referred to as periampullary cancers, may derive either from the pancreatic head, the distal part of the common bile duct, the papilla of Vater itself, or the duodenum. Pancreatic cancers are predominant in this group, and also have the poorest prognosis (1). The late presentation, aggressive local growth and potential for metastasizing make pancreatic cancer one of the most malignant cancers of the gastrointestinal tract. Differentiation between pancreatic cancer and benign conditions, in particular chronic pancreatitis, is a great challenge to the clinician and a critical part in the clinical decision making (2). Since it is impossible to get a correct pathological diagnosis without a biopsy sample and risking local spread, patients with mass lesions in the pancreatic head are usually managed primarily according to the same routine until the decision concerning surgery is taken, irrespective of the origin. Furthermore, as the tumours may be difficult to localize, the biopsy may give a false negative result. In order to

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provide an optimal basis for treatment decision before pancreatic resection is attempted, the patients usually undergo imaging, for example with computer tomography (CT), abdominal ultrasonography, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasonography. The aim of these investigations is to determine whether the tumour is localized and hence resectable. However, despite a thorough preoperative investigation, it is still difficult to distinguish between a malignant tumour and a benign lesion in the pancreatic head, in particular chronic pancreatitis.

Tumour markers, especially carbohydrate antigen 19-9 (CA 19-9), have been suggested as diagnostic aids in patients with suspected periampullary tumours. They may also serve as prognostic factors. Prediction of the prognosis in patients with pancreatic cancer may help to distinguish between those who might benefit from aggressive surgery or chemotherapy and those who would only risk the side effects of such treatment without prolonging survival.

Several markers have been proposed as diagnostic and prognostic markers in patients with periampullary cancer, including Carbohydrate antigen 19-9 (CA 19-9), Tissue polypeptide specific antigen (TPS), Carcinoembryonic antigen (CEA) and Vascular endothelial growth factor (VEGF-A)

CA 19-9 is a glycoprotein which was first suggested as a marker for colon cancer (3). It is the most extensively used marker for pancreatic cancer and is often considered as the golden standard against which other markers can be compared (4). Although CA 19-9 has a high sensitivity for pancreatic cancer, its clinical utility is limited by the fact that its concentration is also elevated in patients with obstructive jaundice of benign causes (5).

TPS is a cytokeratin belonging to the intermediate filament protein group, which forms a part of the cytoskeleton. It constitutes the M3 specific epitope of tissue polypeptide antigen (TPA), which was described 50 years ago (6). As it is more specific than TPA, it has been found useful as a marker for several malignancies, including breast cancer (7), prostate cancer (8) and ovarian cancer (9). Whereas most tumour markers correlate with tumour burden, TPS reflects tumour growth activity. The main clinical utility of TPS is therefore usually considered to be in monitoring treatment and providing an early clinical indication of recurrence (10).

CEA is an acid glycoprotein which is present in the periphery of the tumour cell membrane, where it is released into surrounding body fluids. It is mainly secreted by digestive glandular cancers and their metastases. It is one of the most widely used markers for colorectal cancer, and has also been suggested as a marker for pancreatic cancer (11).

In recent years considerable attention has been paid to angiogenesis as a crucial prerequisite for tumour spread (12). The ability of a tumour to stimulate vascularisation is of fundamental importance for its ability to expand locally as well as to metastasize. The expression of pro-angiogenetic factors has therefore been suggested as a measure of the malignant potential of a cancer. VEGF, also called VEGF-A, is one of the most critical components in angiogenesis. VEGF is a group of angiogenic polypeptides that are involved in angiogenesis and plays a crucial

role in the development and metastasis of various carcinomas. It has been suggested as a marker of tumour progression in pancreatic cancer (13, 14).

The purpose of the present study was to evaluate the abilities of TPS, CA 19-9 and CEA to distinguish between malignant and benign conditions in patients diagnosed with lesions in the pancreatic head and to assess the prognostic value of pre-treatment levels of these markers and of VEGF-A in the long-term follow-up of patients with pancreatic cancer.

Materials and methods

The patients were recruited from the department of surgery of Uppsala University Hospital, an academic tertiary referral centre, from 1997 to 1999. Inclusion criteria were mass lesion in the pancreatic head visualised by any imaging modality or obstruction of the common bile duct in the absence of gallstones. Patients with mass lesions in the pancreatic head were managed according to the ordinary local guidelines. In addition, serum was obtained and stored in a freezer at -30°C . The blood samples were taken from patients admitted for jaundice or other symptoms that raised suspicion of pancreatic cancer. The diagnosis was not known at the time when the samples were taken. In a retrospective review of the patients' histories, the diagnosis, the results of liver tests, including total bilirubin, alkaline phosphatase (ALP), Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) on the sampling occasion, and the date and cause of death were abstracted from the patients' records.

Assay methods

TPS was analysed on an Immulite instrument (Diagnostic Products Corporation, Los Angeles, CA, USA). The total coefficients of variation of the instrument for the analytes were 6.9% at 91 U/L and 4.2% at 415 U/L.

CEA was analysed on a Modular E170 (Roche Diagnostics, Mannheim, Germany). The total coefficients of variation of the instrument for the analytes were 2.6% at 3.62 $\mu\text{g/L}$ and 1.7% at 22.80 $\mu\text{g/L}$. Ca 19-9 was analysed on a Modular E170 (Roche Diagnostics, Mannheim, Germany). The total coefficients of variation of the instrument for the analytes were 2.9% at 9.7 kU/L and 2.8% at 39 kU/L.

Samples for VEGF-A were assayed with commercially available ELISA kits for VEGF-A, (DVE00, R&D Systems, Minneapolis, MN). Briefly, the micro-titre plates had been coated with monoclonal antibodies specific for VEGF-A and the first step was to add standards and samples to the wells. During the following incubation period the VEGF-A present in the standards and samples was bound to the immobilized antibody. After a thorough wash an enzyme-linked polyclonal antibody specific for each protein was pipetted into the wells and after a second incubation and wash step a substrate solution was added and colour developed in proportion to the amount of antigen bound. The colour development was subsequently stopped and the colour intensity was measured by photospectrometry. The results

were calculated according to the manufacturer's recommendations. The inter-assay coefficient of variation was approximately 7%.

Study design

The patients in the study were included prospectively according to the criteria mentioned above. The final diagnosis achieved through pathoanatomical examination was used for validation in the assessment of the markers as diagnostic tools.

Statistical analysis method

Receiver Operating Characteristic (ROC) curves depicting the ability to discriminate between benign and malignant conditions were plotted for each of the markers. Kaplan Meier statistics were calculated by dividing all patients with pancreatic cancer into two groups, with the median level of each marker as cut-off level. The Kaplan Meier statistics were based on overall survival.

Result

Serum samples were taken from 56 patients, 30 men and 26 women. Mean age was 63 years (range 35–92 years, standard deviation [SD] 13 years). Mean age for patients with malignant conditions was 65 years (SD 15 years) and for patients with benign conditions 61 years (SD 11 years). The diagnoses, abstracted in the retrospective review of the patient records, were malignant in 32 cases, including pancreatic ductal adenocarcinoma (N=20), hepatocellular carcinoma (N=2), malignant lymphoma (N=1), cancer of the papilla of Vater (N=5), duodenal cancer (N=1), rectal cancer metastasis (N=1), small cellular cancer of unknown origin (N=1), and metastasis of adenocarcinoma of unknown origin (N=1). None of the patients with pancreatic cancer underwent surgery with a curative aim. Twenty-four patients had benign diseases, including benign stricture of the common bile duct (N=1), chronic cholecystitis (N=1), hamartoma of the common bile duct (N=1), benign gallbladder adenoma (N=1), chronic pancreatitis (N=5), abdominal pain of unknown cause without a malignant diagnosis (N=1), and various benign conditions (N=14).

Median CEA in all patients was 4.0 µg/L (SD 90.3 µg/L), median CA 19-9 137.0 kU/L (SD 204 000 kU/L), median TPS 120.5 U/L (SD 577.3 U/L) and median VEGF-A 131.0 ng/L (SD 802.8 ng/L). In patients with benign conditions, median CEA was 2.2 µg /L (SD 1.7 µg/L), median CA 19-9 33.6 kU/L (SD 195.0 kU/L), median TPS 36.5 U/L (SD 116.4 U/L) and median VEGF-A 60 ng/L (SD 767 ng/L). In patients with malignant conditions median CEA was 6.3 µg/L (SD 102.7 µg/L), median CA 19-9 414 kU/L (SD 234 000 kU/L), median TPS 156 U/L (SD 651 U/L) and median VEGF-A 173 ng/L (SD 830 ng/L). ROC curves for the abilities of CEA, CA 19-9 and TPS to distinguish between benign and malignant diagnoses are plotted in Figures 1–3 respectively. Area under the curve (AUC) was 0.747 (standard error [SE] =0.075) for CEA, 0.716 (SE=0.078) for CA 19-9 and 0.822 (SE=0.086) for TPS. In case patients with pathological ALP (>10 µkat/L) or patho-

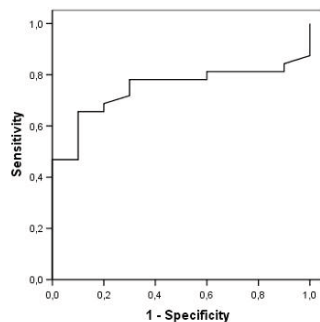


Figure 1. ROC curve for CEA. AUC=0.747, Standard error=0.075

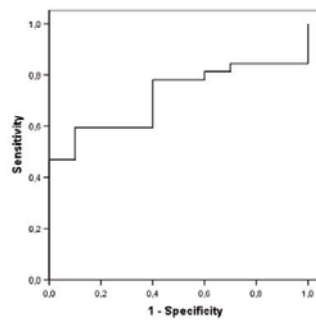


Figure 2. ROC curve for CA 19-9. AUC=0.716, Standard error=0.078.

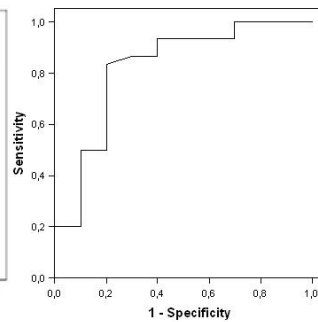


Figure 3. ROC curve for TPS. AUC=0.822, Standard error =0.086

logical bilirubin ($>50 \mu\text{mol/L}$) were excluded, the AUC for CA 19-9 increased to 0.78 (SE=0.097). There was no significant difference between the AUCs for the respective markers.

The log-rank test did not show any significant differences in survival when stratifying the pancreatic cancer group in patients with levels higher and lower than the median of each of the markers.

AST and ALT correlated significantly with CA 19-9, TPS and VEGF-A (all $p < 0.05$), but not with CEA. ALP correlated significantly with TPS ($p < 0.05$) but not with any of the other markers. Bilirubin did not correlate with any of the markers.

Discussion

Our study has shown that the markers investigated may serve as complements to imaging techniques, although the sensitivity and specificity were too low for them to be useful for screening purposes or as a replacement of other diagnostic modalities. Whereas the tested markers may be of some clinical utility, their ability to predict survival in patients with pancreatic cancer was too poor for them to serve as basis for treatment decisions. This is in accordance with the conclusion from previous studies that the value of tumour markers in early disease is questionable, since the presence of a significant tumour burden is required before the levels are sufficiently high to predict the prognosis (15).

Results of previous studies on the diagnostic utility of CA 19-9 have been contradictory. In some studies CA 19-9 has been found to be superior to TPS (16–18), whereas in another study the contrary was shown (19). We found that the AUC was slightly higher for TPS than for CA19-9 and CEA, but the differences were not significant.

A major problem with the use of tumour markers in clinical practice is the poorer sensitivity and specificity for the smallest tumours (20). The utility of a marker depends on its ability to detect tumours when they are still of such a size as to be sur-

gically resectable. The improved resolution and quality of the imaging techniques used to diagnose pancreatic cancer and their increased accessibility in recent years may lead not only to diagnosis of an increased number of benign changes, but also possibly to earlier diagnosis of pancreatic tumours. Although this may increase the chance of cure, it will inevitably reduce the AUC of the markers.

None of the patients with pancreatic cancer in our study underwent pancreatic resection with the aim of radical cure. The decision as to whether to perform radical surgery relies not only on the total tumour burden but also on the localization of the tumour and its relation to the surrounding vessels. In our sample, all patients were found to either have to extensive local growth, metastases or were too old or in a too poor condition to benefit from surgery. The tumour markers are rather crude measures of resectability and prognosis in patients with pancreatic cancer. Despite the fact the marker levels in our study were overall slightly lower than in previous studies of the same markers applied as diagnostic (17,19, 21,22) and prognostic markers (4,10,14, 23), none of the included patients were found to fit for pancreatic resection.

One potential cause of bias would be an increase in the tumour marker levels due to hepatic failure. We found that ALT and AST correlated significantly with all markers except CEA. However, there was no correlation between bilirubin and the tumour markers. This indicates that the levels may be affected more by hepatocellular failure than by obstructive jaundice, which is a frequent finding in patients with mass lesions in the pancreatic head. Whereas ALT are hepatocellular markers; ALP is a marker of bile duct epithelium. A correlation between ALP and the tumour markers would thus have indicated an association with obstruction in the bile ducts. In a previous study it was shown that compromised liver function, irrespective of its cause, increased the serum levels of glycoproteins, including TPS and CA 19-9 (16). A way of avoiding this shortcoming of glycoproteins as markers in patients with obstructive jaundice that may increase their clinical utility would be to repeat the test after the jaundice has been relieved in the event an elevation of TPS or CA 19-9 occurs (20). In our sample, we saw a slight increase in the AUC for CA 19-9 in case patients with pathological bilirubin or ALP were excluded.

Despite the somewhat limited diagnostic and prognostic abilities of tumour markers in small size tumours, the urgent need for effective, inexpensive and easily accessible tools for early diagnosis and staging of tumours in the pancreatic head still makes research on tumour markers worthwhile. Although the markers investigated have not shown sufficient specificity and sensitivity to be useful as the sole base for diagnosis and therapeutic decision until pathological confirmation is obtained, the advent of mass spectrometry may result in a renaissance of peptides as markers for pancreatic cancer. By combining multiple protein markers, it may prove possible to identify a "protein signature" that is superior to each of the specific peptide markers in pancreatic cancer. In a recent study of proteomic profiling, 154 proteins with the potential to distinguish patients with pancreatic cancer from controls were identified (24). Perhaps further studies may prove some of these proteins to be more useful than the markers presently studied.

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