Review

Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer

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Abstract

Background: Although many biochemical markers have been examined in pancreatic cancer none are definitive for pre-operative diagnosis. This systematic review examines studies using biochemical markers for the diagnosis of pancreatic cancer in order to appraise their role in contemporary management algorithms.

Methods: A search of the MEDLINE database was undertaken using the key words pancreatic neoplasm and serum tumour marker. Only studies providing original data on sensitivity and specificity are included and data are presented on diagnostic accuracy, effect of cholestasis and the relation of tumour stage to blood levels of markers.

Results: CA 19-9 is the most extensively evaluated with pooled data from 2283 patients. The median sensitivity of CA 19-9 for diagnosis is 79 (70–90%) and median specificity 82 (68–91%). CA 19-9 elevation in non-malignant jaundice results in a fall in specificity. Combination with other markers improves accuracy.

Conclusion: As the most extensively evaluated marker, CA 19-9 should be used in contemporary algorithms for the diagnosis of pancreatic cancer. Elevated values should be repeated after relief of jaundice.

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Keywords: Serum tumour markers; Pancreatic neoplasm; CA 19-9; CA 50; CEA

Review criteria

Literature search and data extraction strategy

A computerised search was made of the MEDLINE database for the period from January 1990 to December 2005 inclusive. The OVID search engine (Version 9; Ovid Technologies, New York, NY, USA) was employed. The MESH headings Pancreatic neoplasm, diagnosis, CA19-9, CA 50, CEA, Dupan-2, Span-1, Serum tumour markers were used. The search was restricted to articles in English and documents relating to humans. This resulted in 348 hits. The abstracts of these reports were then retrieved and studied. At this stage, studies were excluded if they were case reports, review articles and reports not providing data on serum tumour markers in pancreas cancer. These exclusions resulted in a final study population of 26 manuscripts providing original data on biochemical markers for the diagnosis of pancreatic cancer. Data were extracted in the following categories: number of patients with pancreatic cancer, number with histological confirmation of malignancy, proportion of patients with jaundice, composition of control group (including proportion with jaundice in control), cut-off points for markers, type of assay used for marker analysis, sensitivity, specificity and finally positive and negative predictive value. All extracted data were crosschecked between authors to rule out discrepancy. Particular attention was paid to histological confirmation of malignancy: unless a report specifically mentioned that there was a tissue diagnosis either by biopsy or resection, the diagnosis of pancreatic cancer was not regarded as histological confirmed for the purposes of this study. Data are presented in the following categories: CA 19-9 in the diagnosis of pancreatic cancer, other markers for pancreatic
cancer, effect of cholestasis on diagnostic accuracy and relation of tumour stage to blood levels of markers.

Introduction

A wide range of biochemical tumour markers has been reported to be elevated in patients with pancreatic cancer.1–6 These include tests based on monoclonal antibodies raised against tumour-associated glycoproteins such as carbohydrate antigen (CA 19-9)7 and carbohydrate antigen 242 (CA 242)8, to tests based on the detection of tumour isoenzymes such as tumour-M2-pyruvate kinase (Tu-M2-PK)9,10 and oncofetal antigens.11 The presence of a wide range of tests is an indicator that there is no single definitive diagnostic test for pancreatic cancer. Practical application of diagnostic tests has been limited by the confounding effect of co-existent jaundice on accuracy.12–16 Efforts to circumvent these problems have included the use of tests in combination17–19 or a bank of diagnostic tests.20,21

The relative paucity of development in serological diagnosis of pancreatic cancer has occurred in the context of major advances in diagnosis based on cross-sectional22–24 and endoscopic imaging.25–27 Current pre-operative diagnosis of pancreatic cancer relies on high-resolution, contrast-enhanced computed tomography22 with evidence that contrast-enhanced computed tomography can provide complementary information.25

Given the heterogeneous nature of the studies on biochemical markers for diagnosis of pancreatic cancer, uncertainty remains over the optimal test, timing of sampling and the role of serological markers in surveillance. In this setting, structured systematic reviews may provide information on consistent trends gleaned from a series of studies. Thus the aim of this study is to undertake a systematic review of biochemical markers used in the diagnosis of pancreatic cancer to examine the relative place of these tests in contemporary management algorithms.

Carbohydrate antigen (CA 19-9)

CA 19-9 is a predominantly carbohydrate antigen which was defined from the culture medium of a colorectal cancer cell line. It is a high molecular weight glycolipid derived from a monoclonal antibody isolated from mice, which is immunised with a human colon cell line. Twenty-two reports3,12,18–20,28–44 address the role of CA 19-9 in the diagnosis of pancreatic cancer. With the sole exception of Jang’s study18, all reports use radioimmunoassay for measurement of CA 19-9 (Jang’s report utilizes an enzyme-linked immunosorbent assay ELISA). Data are reported on 2283 patients in whom there was unequivocal histological confirmation of malignancy in 945 (41%). The median sensitivity of CA 19-9 for the diagnosis of pancreatic cancer examining pooled data from all series is 79 (70–90%). The median specificity is 82 (68–91%). The median positive predictive value (PPV) is 72 (41–95) and the median negative predictive value is 81 (65–98).

Carbohydrate antigen CA 242, carbohydrate antigen CA 50, carcinoembryonic antigen (CEA), SPAN-1 and sialyl-lact-N-tetraose (DUPAN-2)

CA 242 is a cancer associated glycoconjugate expressed in mucin and found predominantly in the sera of pancreatic cancer patients. It is a sialylated carbohydrate antigen co-expressed with CA 50, and situated in the same macromolecule. Ten reports3,18,30,32,38,39,44–47 examine the diagnostic accuracy of CA 242 in a total of 806 patients. From pooled data, the median sensitivity of CA 242 is 75 (65–82%), and the median specificity 90 (65–95%). The median PPV is 83 (37–96) and the median NPV 74 (52–96).

CA 50 which may present as a high molecular weight glycolipid or glycoprotein was first identified in 1983. It is detected in a number of epithelial tumours as well as in normal adult pancreatic and gallbladder tissue. Nine reports20,29,30,32,34,36,45–47 examine the diagnostic accuracy of CA 50 in a total of 1137 patients. From pooled data, CA 50 has a median sensitivity of 83 (65–96%) and a median specificity of 73 (34–90%) for the diagnosis of pancreatic cancer with a median PPV of 72 (26–95) and median NPV of 79 (61–99).

Span-1 is a high molecular weight glycoprotein recognized by a murine monoclonal antibody produced against a human pancreatic cell line. Its epitope includes a sialic acid-like CA 19-9. A sandwich radioimmunoassay has recently been developed and clinically tested for this marker. Span-1 (4 reports on a pooled total of 952 patients)28,29,36,37 has a median sensitivity of 82 (81–89%) and a median specificity of 83 (67–85%). The median PPV is 50 (45–88) and median NPV is 93 (77–98).

Dupon-2 is a monoclonal antibody raised against a human pancreatic adenocarcinoma cell line. The epitope of Dupan-2 antigen (sialyl-lact-N-tetraose) is a glycosylated antigen expressed on a mucin like molecule, and is the precursor of CA 19-9. Dupan-2 (4 reports, 798 patients)12,20,28,36 has a median sensitivity of 65 (48–80%) and a median specificity of 80 (75–85%). The median PPV is 68 (45–83) with a median NPV of 78 (60–89).

Carcinoembryonic antigen is a heterogeneous group of glycoproteins containing 50–80% carbohydrates and a single protein chain of about 800 amino acids. CEA (13 reports, 1323 patients)8,12,20,28,35,37,40,43–45,48 shows the lowest median sensitivity of 54 (40–92%) and a median specificity of 79 (59–90%). The median PPV is 65.5 (25–91) and median NPV is 72 (53–98).

Effect of jaundice on sensitivity and specificity in pancreas cancer

Three of four12,31,40,41 studies comparing CA 19-9 for diagnosis of pancreas cancer either in the presence or
absence of jaundice show that jaundice was associated with increased sensitivity. However, any benefit is offset by all studies showing a fall in specificity in the presence of jaundice. Ohshio’s study shows that similar findings were seen with CEA and Dupan-2.12

Results for the interpretation of CA19-9, CEA and Dupan-2 in the presence of cholestasis are shown for the studies available.

**Effect of tumour stage on accuracy of tumour markers (UICC TNM classification)**

Ten studies18,29,31,36,38–40,44,48 examined the effect of tumour stage on the accuracy of tumour markers (nine evaluated CA 19-9 either alone or in combination). In all studies, the trend was for greater sensitivity with advancing stage of cancer at the time of initial presentation.

**Discussion**

A tumour marker that allows for the reliable diagnosis of pancreatic cancer has proved elusive. Many studies have examined markers in a large number of patients but despite this it remains difficult to draw definitive conclusions. This systematic review has examined the available reports on the use of biochemical markers for the diagnosis of pancreatic cancer. The search parameters and history are described so that the yield can be independently duplicated. As with all systematic reviews it remains possible that studies containing potentially valuable data may not have eluded detection. Other potential limitations include publication bias in favour of studies reporting positive data and the risk of compounding inaccuracy when pooling predictive data (sensitivity and specificity). Acknowledging these limitations, an important strength of this systematic review is that it highlights the considerable variation in study design and composition of patient cohorts that exists between studies. Key variations are in the nature of the control group (non-pancreatic cancer controls pooled with non-cancer controls), the rigour used to obtain a tissue diagnosis of malignancy in patients with suspected pancreatic cancer and in the proportion of patients with jaundice. There are also considerable variations in the cut-off values used to distinguish the normal range.

Considering these limitations, what can be learnt from this study, thought to be the largest pooled cohort data report on the utility of biochemical markers for the diagnosis of pancreatic cancer? First, it is readily apparent that CA 19-9 is the most thoroughly evaluated test. With an overall pooled sensitivity from 2283 patients of 79% and a specificity of 82% across a range of reports over a relatively prolonged period of time it is the standard for comparison of other tests. The principal limitation of CA 19-9 is that it can be elevated in patients with non-malignant obstructive jaundice resulting in impaired specificity. Efforts to circumvent this limitation include the use of higher cut-off values31 (300 U/ml increases the specificity to 87% in patients with cholestasis) and the use of an array of tumour markers. There is no additional advantage in sampling bile CA 19-9 as the bile to serum ratio is 1:1.12 Knowledge of the Lewis blood group status may aid interpretation of CA 19-9 in cancer as Rosen reported that the 10% of the Caucasian population who are Lewis genotype negative are unable to express CA 19-9.34 Serial CA 19-9 analysis after relief of jaundice may be useful although in Ohshio’s study, CA 19-9 remained elevated. In an interesting report, Malesci and colleagues reported that a normal CA 19-9 combined with normal imaging effectively ruled out pancreatic cancer. A further study done by Ritts and colleagues combining diagnostic imaging and preoperative CA19-9 levels suggest CA19-9 to be a good adjunct when combined with radiological imaging in non-jaundiced patients.49 In 84 patients with histologically confirmed pancreatic cancer, CA19-9 values >40 u/ml in the presence of positive or equivocal radiological findings was highly suggestive of a diagnosis of pancreatic cancer. (positive predictive value 0.94). These findings are worthy of further study.

A common approach is to utilize CA 19-9 in combination with other markers. It is difficult to draw conclusions from these reports but individual studies have suggested that the addition of CAM 17.1/WGA31 or CA 24232 increased diagnostic yield. More dramatically, composite marker systems such as CAMPAS-P, which are based on CA 19-9 plus 9 other markers, differentiated all 35 cancers from the 32 patients with benign disease in Saito’s study.

The sensitivity of biochemical markers is increased in patients with advanced disease but in contemporary hepato-pancreato-biliary practice it would be expected that these patients would be readily identified by imaging modalities.

Increasing evidence suggests that Tu-M2-PK may become a valuable plasma marker for the diagnosis of cancer. Numerous investigators have reported on the utility of Tu-M2-PK in the early diagnosis of pancreatic cancer. The sensitivity (71%–79%) and specificity (64%–95%) reported in various series were encouraging.50–54 Tu-M2-PK has an advantage over CA19-9 in that it is not affected by cholestasis. The potential promise of tumour metabolism-based markers such as Tu-M2-PK as markers of disseminated malignancy in patients with no overt evidence of metastasis require further study.55

Finally, although several studies have examined the role of CA 19-9 as a population screening tool56–58 it is not sufficiently reliable for this role.

There have been large studies done in Japan and Korea to assess the usefulness of CA19-9 as screening tool to diagnose pancreatic cancer in both asymptomatic and symptomatic patients.

Mass screening was conducted in Japan over two different periods, 1984–1985 and 1987–1988 on asymptomatic and symptomatic outpatients, all over 40, in 17 hospitals. All patients underwent either US or serum CA19-9 and
elastase 1 levels. When results were abnormal, further studies were carried out, including repeat US, ERCP, CT etc. A final diagnosis was made either clinically or histologically. Mass screening of 10 162 asymptomatic persons >40 resulted in the detection of only 4 cases of pancreatic cancer. A screening of 2678 asymptomatic persons >40 in another later survey produced no cases of pancreatic cancer. By contrast, in screening 4506 symptomatic outpatients >40, they found 85 pancreatic cancers (2%) of which 28 (32%) were resected. 56 of more than 4200 symptomatic outpatients (1%) in the later survey were diagnosed with cancer of pancreas, 19 (34%) of whom underwent resection. Similar study undertaken in Korea involving 70 940 asymptomatic patients detected only 4 patients with pancreatic cancer. Therefore, using serum CA19-9 with US to detect pancreatic cancer through mass screening is ineffective in asymptomatic patients but effective to screen symptomatic outpatients in finding resectable tumours.

In summary, the recommendations made as a result of this systematic review are that CA 19-9 as the most thoroughly evaluated biochemical marker should be used in current management algorithms. Intelligent, contemporary use of CA 19-9 would suggest that elevated values be repeated after relief of jaundice (bearing in mind that false positives may persist), higher cut-offs considered in jaundiced patients and a normal CA 19-9 taken to add weight to the exclusion of pancreatic cancer in a patient with normal cross-sectional imaging. Although other markers have been evaluated, none at present can be regarded as consistently superior to CA 19-9. A final important lesson to learn from this systematic review is that future studies must look to obtain a diagnosis of cancer more rigorously and pay greater detail to protocol design in terms of inclusion of jaundiced patients and the nature of the control group.

References


