Original article

Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas

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Background: **Intraductal papillary mucinous neoplasm (IPMN) of the pancreas has malignant potential. Although serum levels of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) are known to be raised in pancreatic ductal adenocarcinoma, little has been reported about their significance in IPMN.**

Methods: **Preoperative CA19-9 and CEA levels were measured in consecutive patients undergoing surgical resection for IPMN. Results were correlated with histopathological and clinical features.**

Results: **In 142 patients, raised CEA and CA19-9 serum levels were significantly associated with invasiveness in both branch-duct and main-duct/mixed-type IPMN. Some 74 per cent of patients with an invasive IPMN had raised levels of CA19-9, compared with only 14 per cent who had non-invasive tumours. With a cut-off level of 37 units/ml, CA19-9 had a specificity of 85·9 per cent, a negative predictive value of 85·9 per cent, a positive predictive value of 74·0 per cent and accuracy of 81·7 per cent. Overall, 80 per cent of patients with an invasive IPMN had raised serum levels of CA19-9 and/or CEA compared with only 18 per cent of those with a non-invasive tumour ($P < 0·001$).**

Conclusion: **Serum CA19-9 is a useful non-invasive preoperative tool for differentiating between invasive and benign IPMN, and should be taken into account in the decision to offer surgery. Patients with an IPMN and positive tumour markers have a high risk of malignant disease.**

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Introduction

Intraductal mucinous neoplasms (IPMNs) of the pancreas are well described cystic tumours characterized by mucin production and malignant potential[1,2]. In contrast to pancreatic ductal adenocarcinomas, IPMNs are slow-growing tumours that are often diagnosed incidentally before causing symptoms[3]. Conservative management with yearly follow-up has been proposed for asymptomatic smooth-walled branch-duct IPMN less than 3 cm in diameter without mural nodules[4,5]. However, histologically malignant features (carcinoma *in situ* or invasive cancer) are found in resected surgical specimens of approximately 25 per cent of branch-duct and 70 per cent of main-duct IPMNs[2]. The management of IPMNs as precursor lesions offers the possibility of detecting early stages of malignant progression with the opportunity to improve outcome by timely intervention.

In many patients, the decision between surgical resection and surveillance is challenging, especially in those with multiple cystic lesions, chronic pancreatitis and pseudocysts, as well as elderly patients with multiple co-morbidities. Accurate diagnosis and preoperative assessment are crucial[6]. Even with modern cross-sectional imaging it remains difficult to predict malignancy correctly[7].

Levels of carbohydrate antigen (CA) 19-9, a tumour-associated glycoprotein, are raised in approximately 85 per cent of patients with pancreatic ductal adenocarcinoma[8]. Serum CA19-9 measurement can be used for diagnostic purposes, as a predictor of resectability[9] or as a marker of recurrent disease after resection[8,10]. Carcinoembryonic antigen (CEA) is a 180-kDa cell surface glycoprotein whose levels are increased in more than 60 per cent of patients with pancreatic ductal adenocarcinoma[10]. It is released from the periphery of the

cancer cell membrane into surrounding body fluids and subsequently into the systemic circulation. In obstructive jaundice, serum levels of both these tumour markers can be increased as a result of reduced biliary excretion[11].

In patients with resectable ductal adenocarcinoma, raised serum levels of CA19-9 and CEA have been shown to predict stage and survival[12–14]. Fine-needle aspiration of pancreatic cyst fluid and evaluation of tumour markers has been used for positive diagnosis and prediction of malignancy in IPMNs[7]. The significance of these markers in the serum of patients with IPMN is not known[15].

The aim of the present study was to evaluate the ability of serum CA19-9 and CEA levels to distinguish correctly between benign and invasive IPMNs. Knowledge of a high risk of malignancy may simplify clinical decision making in patients with IPMN.

Methods

Consecutive patients with an IPMN who underwent surgical resection at the Department of Surgery, University Hospital of Heidelberg, between 1 July 2004 and 31 December 2008 were included in the study. The indication for resection was based on symptoms and radiological findings. Main-duct and mixed-type IPMNs were resected regardless of size. Branch-duct IPMNs were resected if larger than 3 cm, mural nodules were present, the main pancreatic duct was dilated to more than 6 mm, or the patient had symptoms. In addition, patients who were concerned about a risk of malignant transformation were offered surgery regardless of cyst size. All patient data were entered prospectively into a database. Inclusion criteria for the present study were: histologically proven IPMN in the surgical specimen, preoperative serum levels of CA19-9 and CEA available, no previous surgery for IPMN and absence of preoperative jaundice (serum bilirubin level less than 34·2 μmol/l).

Histology was assessed using the internationally accepted definition for IPMN[16]. IPMNs were first classified into invasive and non-invasive types. Surgical specimens without an invasive component were subclassified into three histological grades in accordance with the current classification system[17]: IPMNs with low-grade dysplasia (adenoma), those with moderate dysplasia (borderline) and those with high-grade dysplasia (carcinoma *in situ*). Additionally, based on the pathological examination and histology, IPMNs were subclassified into main-duct, branch-duct and mixed type.

Laboratory results were reviewed for preoperative serum CA19-9, CEA and total bilirubin levels determined simultaneously within 3 days before surgery. All blood samples were analysed for tumour markers at the routine laboratory of the University Hospital of Heidelberg using an electrochemiluminescence-based assay (Elecsys® 2010; Roche Diagnostics, Mannheim, Germany).

CA19-9 levels of 37 units/ml or less were considered to be in the normal range. As CEA values are considered normal when lower than 2·5 μg/l in non-smokers and lower than 5 μg/l in smokers[18], a cut-off level of 5 μg/l was used. Serum values of CEA were considered normal when below 5 μg/l.

Statistical analysis

Tumour marker values are presented as median (interquartile range). The distribution of each tumour marker was presented graphically as a box and whisker plot. Differences between subgroups with respect to the tumour markers were analysed using the Mann–Whitney *U* test. Fisher's exact test was used to compare subgroups of patients. The correlation between tumour markers was examined using the Spearman correlation coefficient, r_s. Sensitivity, specificity, positive and negative predictive values, and accuracy were calculated by choosing the normal ranges of CEA and CA19-9 as cut-off levels. To analyse the relationship between sensitivity and specificity over all possible cut-off values of CEA and CA19-9, receiver operating characteristic (ROC) curves were created using logistic regression models. Unless indicated otherwise, two-sided tests were used. Statistical significance was accepted at the 5 per cent level ($P \leq 0{\cdot}050$). Statistical evaluation of the data was performed using SAS® version 9.1 for Windows® (SAS Institute, Cary, North Carolina, USA).

Results

Among a total of 172 patients with an IPMN, 165 had preoperative CA19-9 and CEA values documented. Five patients were excluded because they underwent surgery for recurrent disease. Some 18 patients with extrahepatic cholestasis, determined by a serum bilirubin level of at least 34·2 μmol/l, were excluded from the main study to avoid the confounding effect of hyperbilirubinaemia.

Some 142 patients (82 men and 60 women, age range 31–87 years) were included in the study. Of these, 92 had benign disease or high-grade dysplasia and 50 had invasive ductal adenocarcinoma arising in an IPMN. Of those with a non-invasive IPMN including carcinoma *in situ*, 37 presented with low-grade, 38 with moderate and 17 with high-grade dysplasia. Considering all 142 IPMNs, 51 (35·9 per cent) were branch-duct type, 16 (11·3 per cent) main-duct type and 75 (52·8 per cent) mixed type. For

further statistical analysis, main-duct and mixed-type IPMNs were combined (91 patients). With regard to the ductal type, seven (14 per cent) of 51 branch-duct IPMNs had histological characteristics of invasive growth, whereas 43 (47 per cent) of 91 main-duct and mixed-type lesions were invasive ($P < 0{\cdot}001$).

Some 74 per cent of patients (37 of 50) with an invasive IPMN had raised CA19-9 levels compared with only 14 per cent (13 of 92) with a non-invasive tumour. Forty per cent (20 of 50) with an invasive tumour had raised levels of CEA in contrast to only 8 per cent (7 of 92) with a non-invasive IPMN. Overall, 80 per cent of patients (40 of 50) with an invasive IPMN had raised serum levels of CA19-9 and/or CEA compared with only 18 per cent (17 of 92) with a non-invasive IPMN ($P < 0{\cdot}001$) (*Table 1*).

Considering the group with invasive IPMNs, 40 per cent of patients had a raised level of CA19-9 alone, 6 per cent of serum CEA alone, and levels of both tumour markers were increased in 34 per cent (*Table 2*). Using preoperative radiological criteria to predict the risk of malignancy (size, presence of nodules or solid tumour, infiltrative growth, dilated main pancreatic duct, calcification or a central scar), the majority of invasive IPMNs were found to be suspicious for malignancy by preoperative imaging. Seven patients (7 of 50, 14 per cent; including four with a branch-duct IPMN) who did not meet any risk criteria for malignancy in the preoperative evaluation had invasive IPMN on histology. Of these seven, six had a raised level of CEA and/or CA19-9 before surgery.

Lymph node metastases were found in the resected specimen in 27 of 40 patients with an invasive IPMN who had positive tumour markers. In contrast, only three of ten patients with invasive IPMNs and normal tumour markers had positive nodes. The difference did not reach statistical significance ($P = 0{\cdot}067$). Although the majority of invasive IPMNs had positive tumour markers, most of the non-invasive IPMNs had normal markers. There was no statistically significant difference in the incidence of positive tumour markers between the different histological grades of dysplasia among non-invasive IPMNs.

The median CA19-9 concentration among those with an invasive IPMN was significantly higher than that in patients with an IPMN with high-grade dysplasia: 123·7 (32·0–381·3) *versus* 12·8 (5·5–28·7) units/ml ($P < 0{\cdot}001$). In contrast, there was no significant difference in serum CA19-9 levels among patients with non-invasive IPMNs, including those with low-grade, moderate or high-grade dysplasia: 10·3 (6·3–23·6), 10·8 (5·5–27·1) and 12·8 (5·5–28·7) units/ml respectively (*Fig. 1*).

Table 1 Tumour marker levels in relation to histological grade of dysplasia in 142 patients with intraductal papillary mucinous neoplasm

Histological grade	Raised CA19-9 and/or CEA level	*P**
Non-invasive IPMN	17 of 92 (18)	
Low grade	7 of 37 (19)	1·000†
Moderate	6 of 38 (16)	0·786†
High grade	4 of 17 (24)	0·510†
Invasive carcinoma	40 of 50 (80)	< 0·001‡

Values in parentheses are percentages. CA, carbohydrate antigen; CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasm. *Fisher's exact test; †*versus* subgroups of non-invasive IPMNs; ‡*versus* all non-invasive IPMNs.

Table 2 Frequency of raised tumour marker levels in 50 patients with invasive intraductal papillary mucinous neoplasms

CA19-9	CEA	Frequency	Cumulative frequency
Positive	Positive	17 (34)	17 (34)
Positive	Negative	20 (40)	37 (74)
Negative	Positive	3 (6)	40 (80)
Negative	Negative	10 (20)	50 (100)

Values in parentheses are percentages. CA, carbohydrate antigen; CEA, carcinoembryonic antigen.

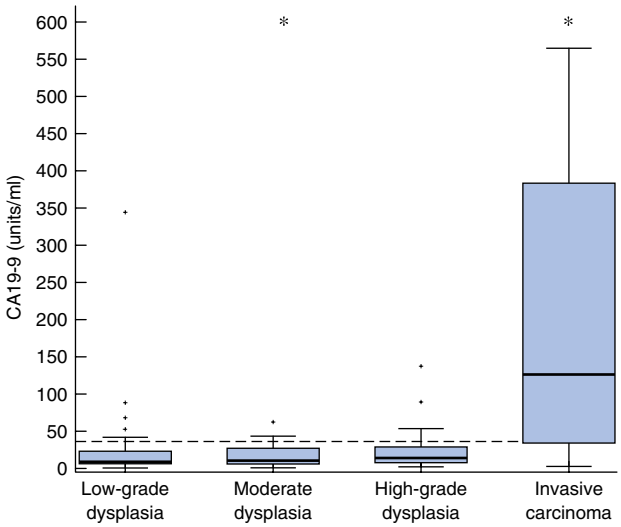

Fig. 1 Box and whisker plots showing serum levels of carbohydrate antigen (CA) 19-9 in relation to histological grade of dysplasia in 142 patients with intraductal papillary mucinous neoplasms of the pancreas. Horizontal lines with boxes, boxes and error bars represent median, interquartile range and range respectively. Values outside the range are represented by crosses. *Some high values are outside the diagram (one in moderate dysplasia group and nine in invasive carcinoma group). The dashed line indicates the cut-off level of 37 units/ml

The serum CEA level was increased to over 5 μg/l in 40 per cent of patients with an invasive IPMN and in 8 per cent of those with a non-invasive tumour. Again, there was no statistically significant difference among non-invasive IPMNs with varying grades of dysplasia: median CEA levels were 1·7 (1·3–2·6), 2·0 (1·1–2·9) and 1·7 (0·9–2·4) μg/l in those with low-grade, moderate and high-grade dysplasia respectively. In contrast, total CEA levels were significantly higher in those with invasive IPMNs (3·6 (2·0–7·5) μg/l) than in patients with a non-invasive IPMN with high-grade dysplasia ($P < 0·001$) (*Fig. 2*).

Differentiating between invasive branch-duct *versus* invasive main-duct/mixed-type IPMN, there was no statistically significant difference in median CA19-9 and CEA levels ($P = 0·899$ and $P = 0·769$ respectively). Considering the group of main-duct/mixed-type IPMNs alone, patients with an invasive IPMN had significantly higher median levels of serum CA19-9 than those with a non-invasive tumour: 121·6 (43·8–381·3) *versus* 11·0 (5·8–27·9) units/ml (one- and two-sided $P < 0·001$). Similarly, invasive cancer arising in a branch-duct IPMN was associated with significantly higher levels of serum CA19-9 than non-invasive branch-duct IPMNs: 254·2 (7·2–1674·0) *versus* 10·6 (6·0–23·6) units/ml (one-sided $P = 0·038$, two-sided $P = 0·075$). Serum CEA levels were also significantly higher in patients with invasive branch-duct IPMNs than in patients with non-invasive branch-duct lesions (one-sided $P = 0·025$, two-sided $P = 0·050$). Thus, in both branch-duct IPMNs and main-duct/mixed-type IPMNs, raised CEA and CA19-9 levels indicated invasiveness.

There was a positive correlation between serum CEA and serum CA19-9 levels ($r_s = 0·466$, $P < 0·001$). Differences were found between possible cut-off levels and the corresponding sensitivity and false-positive rate (1 − specificity) of the two tumour markers. The area under the ROC curve was higher for CA19-9 levels than for CEA levels (0·826 *versus* 0·727), indicating that CA19-9 was a better prognostic marker for distinguishing between malignant and benign IPMNs (*Fig. 3*). Using 37 units/ml as a cut-off level for CA19-9 yielded a specificity of 85·9 per cent, a negative predictive value of 85·9 per cent, a positive predictive value of 74·0 per cent and an accuracy of 81·7 per cent. When the cut-off level of CA19-9 was increased to 70 units/ml, the specificity rose to 94·6 per cent and the positive predictive value to 87·2 per cent, but the sensitivity fell from 74·0 to 68·0 per cent. When the combination of pathological CEA and/or CA19-9 levels was analysed, the negative predictive value increased to 88·2 per cent, whereas the accuracy remained unchanged at approximately 81 per cent (*Table 3*).

Analysis including patients with raised levels of bilirubin showed that 22 per cent of patients (14 of 64) with an invasive IPMN had raised levels of bilirubin, owing to

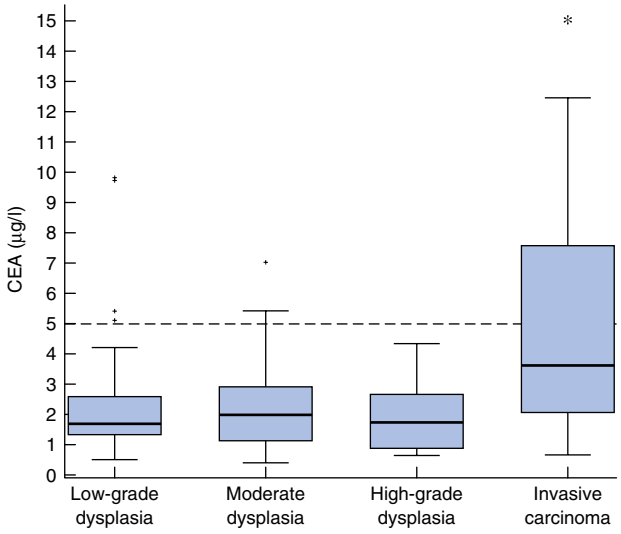

Fig. 2 Box and whisker plots showing serum levels of carcinoembryonic antigen (CEA) in relation to histological grade of dysplasia in 142 patients with intraductal papillary mucinous neoplasms of the pancreas. Horizontal lines with boxes, boxes and error bars represent median, interquartile range and range respectively. Values outside the range are represented by crosses. *Four high values are outside the diagram. The dashed line indicates the cut-off level of 5 μg/l

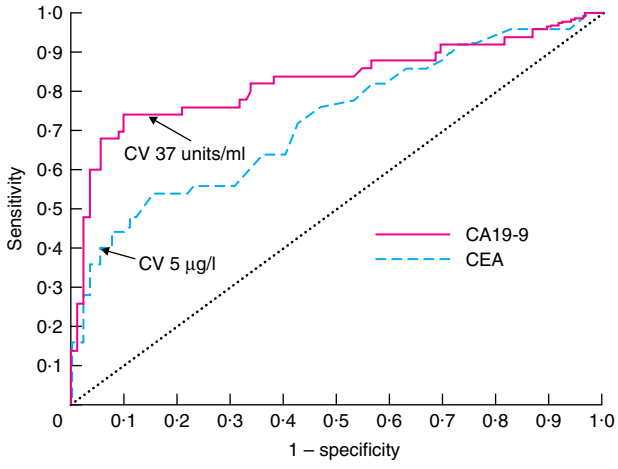

Fig. 3 Receiver operating characteristic (ROC) curves for serum levels of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), showing the relationship between sensitivity and specificity for distinguishing between 50 invasive IPMNs and 92 non-invasive IPMNs over all possible cut-off values (CVs)

Table 3 Diagnostic indices for raised carbohydrate antigen 19-9 and carcinoembryonic antigen levels

	CA19-9	CEA	CA19-9 and/or CEA
Cut-off value	37 units/ml	5 μg/l	37 units/ml, 5 μg/l
Sensitivity (%)	74·0	40·0	80·0
Specificity (%)	85·9	92·4	81·5
Positive predictive value (%)	74·0	74·1	70·2
Negative predictive value (%)	85·9	73·9	88·2
Accuracy (%)	81·7	73·9	81·0

CA, carbohydrate antigen; CEA, carcinoembryonic antigen.

extrahepatic cholestasis, most likely caused by tumour-related biliary obstruction. In contrast, only 4 per cent of non-invasive IPMNs (4 of 96) presented with cholestasis. IPMNs in patients with a bilirubin level exceeding 34·2 μmol/l were more likely to be malignant ($P < 0·001$).

Discussion

The tumour markers CA19-9 and CEA have been investigated extensively in ductal adenocarcinoma for both diagnosis and prognosis[9,13,14,19]. The present study focused on IPMN; serum CA19-9 and/or CEA levels were raised in 80 per cent of patients with an invasive IPMN compared with only 18 per cent of those with a benign IPMN.

Analysis of cyst fluid derived from fine-needle aspiration has also been used to distinguish malignant cystic tumours and potentially premalignant mucinous cystic neoplasms from pseudocysts and serous cystadenomas. Although cyst fluid CEA was the most accurate test available for the identification of malignant cystic lesions of the pancreas[20], cyst fluid CEA and CA19-9 were of limited value in differentiating malignant from benign disease[21]. In contrast to this invasive diagnostic approach, serum concentrations of tumour markers are easy to obtain. The results of the present study reflect previous findings that preoperative assessment of CA19-9 can be useful for the differential diagnosis between pancreatic carcinoma and benign pancreatic diseases in non-jaundiced patients[22], and that a raised CA19-9 level is an independent predictor of malignant IPMN[23].

The correct differential diagnosis between benign and malignant IPMN is crucial for deciding on appropriate management. With small IPMNs, patients with questionable malignancy on cross-sectional imaging or those with multiple co-morbidities, raised levels of tumour markers (CA19-9 over 37 units/ml and/or CEA at least 5 μg/l) may facilitate the decision to proceed with surgical resection instead of conservative management. Resection is indicated for main-duct and mixed-type IPMNs whenever the patient is an appropriate candidate for such surgery, but those with asymptomatic branch-duct IPMNs smaller than 3 cm in diameter without suspicious features of malignancy can be treated conservatively[4]. The present study has shown that serum CEA and CA19-9 levels may also be helpful in the preoperative differential diagnosis between benign and invasive branch-duct IPMNs. In patients with small branch-duct IPMNs, the presence of raised tumour marker levels before surgery might be helpful when radiological imaging does not reveal the common criteria of malignancy.

In addition to prediction of malignancy, increased levels of CA19-9 and CEA in the present study correlated significantly with positive lymph node status in patients with invasive IPMN. Consequently, limited resections, such as enucleation, should not be undertaken in patients with positive tumour markers. Lymphadenectomy should be performed as part of an appropriate oncological resection.

Cholestasis is known to influence serum tumour marker concentrations[24]. Both CA19-9 and CEA undergo biliary excretion, and serum levels might be artificially increased as a result of biliary obstruction caused by IPMN masses. In a number of pharmacokinetic studies, significant alterations in biliary excretion were reported to occur at levels greater than 1·5 times the upper normal limit, or above 34·2 μmol/l[25]. Only patients with a total bilirubin blood serum level of less than 34·2 μmol/l were included in the present study. Because jaundice is known to be a predictor of malignancy in IPMNs[26], cholestasis with or without an increase in tumour markers should prompt the decision to proceed with resection if the patient is fit[22].

A fifth of patients with an invasive IPMN in the present study did not have raised levels of CA19-9 or CEA. CA19-9-associated monoclonal antibody (1116 NS 19-9) reacts with the sialylated Lewis^{ab} blood group substance. Because 5–7 per cent of the population belong to the Lewis^{a-b-} blood group, these patients cannot synthesize the antigen detected by antibody 19-9[27,28]. As there is evidence that a preoperative increase in CA19-9 concentration correlates with stage of disease in ductal adenocarcinoma[10,12], it is possible that most of the antigen produced by small IPMNs is excreted into the duodenum via the pancreatic juice instead of being released into the bloodstream. This would be analogous to the situation in localized colorectal cancer, where most of the tumour markers generated are excreted into the bowel lumen[18]. These observations seem consistent with the finding that normal preoperative levels of CA19-9 are associated with improved survival in patients with resectable ductal adenocarcinoma[29].

Although the sensitivity and specificity of CA19-9 and CEA were too low to make a recommendation for their use as a diagnostic test or for replacing conventional diagnostic imaging, they may serve as complementary tools within the context of preoperative staging investigations of IPMNs by helping to distinguish between benign and invasive tumours.

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