

# Value of preoperative serum CA 19-9 levels in predicting resectability for pancreatic cancer

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**Background:** Pancreatic cancer carries a poor prognosis; at operation approximately 25% of patients will be found to have unresectable tumours even though CT has demonstrated that they are resectable. At our tertiary care centre, we wished to find out if there is an optimum cut-off value for the CA 19-9 level preoperatively that will indicate that the pancreatic cancer is unresectable despite radiologic imaging that suggests otherwise according to receiver operating characteristic (ROC) curve analysis. **Methods:** Preoperative demographic data, clinical features and serum CA 19-9 levels were reviewed for 51 patients with pancreatic cancer who underwent laparotomy between 1998 and 2003. Preoperatively, resectability was determined from a complete history, physical examination and radiologic imaging. An ROC curve was constructed for the CA 19-9 levels. The sensitivity, specificity, positive and negative predictive values of CA 19-9 were calculated with several cut-off points. **Results:** There were 18 (36%) resectable and 33 (64%) unresectable pancreatic cancers. The mean CA 19-9 level was 68.8 U/mL in the resectable group and 622 U/mL in unresectable group. When a CA 19-9 level of 256.4 U/mL was used as a cut-off point, the specificity and sensitivity was 92.3% and 82.4% respectively. **Conclusion:** Preoperative CA 19-9 levels may be a useful marker for determining preoperatively which patients have unresectable disease despite the demonstration on CT of resectable disease.

**Contexte :** Le cancer du pancréas a un pronostic médiocre : au moment de l'intervention, on constate qu'environ 25 % des patients ont une tumeur irrésécable, même si la TDM a indiqué qu'elle était résécable. À notre centre de soins tertiaires, nous voulions déterminer s'il y a une valeur limite optimale de la concentration préopératoire de CA 19-9 qui indiquera que le cancer du pancréas est irrésécable même si l'imagerie radiologique indique que ce n'est pas le cas selon l'analyse de la courbe des caractéristiques opératoires du receveur (COR). **Méthodes :** On a étudié les données démographiques préopératoires, les caractéristiques cliniques et les concentrations sériques de CA 19-9 de 51 patients qui avaient un cancer du pancréas et ont subi une laparotomie entre 1998 et 2003. Avant l'intervention, on a déterminé le caractère résécable à partir d'antécédents complets, d'un examen médical et d'examen d'imagerie radiologique. On a construit une courbe COR pour les concentrations de CA 19-9. On a calculé la sensibilité, la spécificité, les valeurs prédictives positive et négative du CA 19-9 et plusieurs points limites. **Résultats :** On a calculé qu'il y avait 18 (36 %) cancers du pancréas résécables et 33 (64 %) qui étaient irrésécables. La concentration moyenne de CA 19-9 s'est établie à 68,8 U/mL chez les sujets dont la tumeur était résécable et à 622 U/mL chez ceux dont la tumeur était irrésécable. Lorsqu'on a utilisé une concentration de 256,4 U/mL de CA 19-9 comme point limite, la spécificité et la sensibilité ont atteint 92,3 % et 82,4 % respectivement. **Conclusion :** Les concentrations préopératoires de CA 19-9 peuvent constituer un marqueur qui aide à déterminer avant l'intervention les patients qui ont une tumeur irrésécable même si la TDM indique qu'elle est résécable.

The prognosis for pancreatic cancer is grim. Surgical resection represents the only chance for cure, but only 10%–20% of patients are eligible for resection.<sup>1</sup> Thin-cut, con-

trast-enhanced CT has become the study of choice to stage and evaluate a pancreatic cancer.<sup>1,2</sup> CT reliability in predicting resectability ranges from 20% to 90%, but predicts unre-

sectability in almost 100% of cases.<sup>1</sup> Approximately 25% of patients who undergo laparotomy will have unresectable tumours.<sup>3,4</sup>

CA 19-9 has been proposed as a

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useful marker for pancreatic cancer<sup>5,6</sup> and has been reported to have sensitivity ranging from 69% to 93% and specificity ranging from 78% to 98% for detection but is inaccurate for predicting resectability.<sup>1</sup> It is well known that moderately increased concentrations of CA 19-9 can be found in 15%–36% of patients with benign pancreatic, liver and biliary tract diseases.<sup>6</sup>

An efficient way to display and assess the predictive value of a parameter throughout a range of cut-off points is with receiver operating characteristic (ROC) curves. ROC curve analysis is a simple tool to determine the positive cut-off point of a test.<sup>7</sup>

We wished to assess the value of the CA 19-9 level in determining unresectability of pancreatic cancer, according to ROC curve analysis, despite resectable disease demonstrated by CT.

## Methods

At the Fifth Department of Surgery, Ankara Numune Training and Research Hospital, we reviewed the preoperative age, sex, clinical features and serum CA 19-9 levels of 51 patients (28 male, 23 female, mean age 56 years [range 38–74 yr]) with pancreatic cancer and preoperative CA 19-9 measurement whose tumour was deemed operable on the basis of preoperative clinical and radiologic assessment. These patients were admitted between January 1998 and December 2003 and underwent laparotomy. Preoperative resectability was determined on the basis of the clinical evaluation, including complete history, physical examination and radiology (contrast-enhanced dynamic CT with or without endoscopic retrograde cholangiopancreatography [ERCP], with or without percutaneous transhepatic cholangiography). Resectability was defined as a tumour limited to the pancreas without evidence of nodal, peritoneal or hepatic spread and no invasion of

neighbouring vascular structures.

Serum levels of CA 19-9 and total bilirubin were measured preoperatively (normal 0–39.0 U/mL for CA 19-9 and 0–1.71 µmol/L for bilirubin). CA 19-9 levels were measured by the AxSYM CA 19-9 assay kit (Abbott Laboratories) with Microparticle Enzyme Immunoassay technology. CA 19-9 is partially excreted by the biliary route, and a previous study<sup>3</sup> has shown increased serum CA 19-9 levels in the presence of hyperbilirubinemia. In this series, mean total serum bilirubin levels for resectable and unresectable tumours were found to be 23.6 µmol/L and 28.4 µmol/L respectively ( $p > 0.05$ ). Therefore, CA 19-9 levels were not adjusted.

Since there is no staging laparoscopy protocol for pancreatic cancers in our unit, all patients underwent laparotomy. The operation included pancreaticoduodenectomy for resectable lesions, and palliation and biopsy for unresectable lesions with involvement of vital vessels or distant metastasis.

Pancreatic adenocarcinoma was confirmed by pathological examination in all cases. Exclusion criteria were benign disease and cancers known to be of different histologic origin.

## Statistical analysis

All values are expressed as median, mean and standard error of the mean (SEM). Differences in the CA 19-9 and bilirubin levels were tested by the Mann–Whitney–Wilcoxon rank

sum analysis. A value of  $p < 0.05$  was considered statistically significant. An ROC curve was constructed for CA 19-9. The sensitivity, specificity, positive and negative predictive values of CA 19-9 were calculated with several cut-off levels.

## Results

Although all patients were shown by CT staging to have resectable disease, at laparotomy only 18 (35%) tumours were resectable and 33 (65%) unresectable. Of the 33 patients, 18 had metastatic disease and 15 had locally advanced unresectable disease. The mean CA 19-9 level was 68.8 U/mL in the resectable group and 622 U/mL in the unresectable group (Table 1). Differences between the 2 groups were significant ( $p < 0.05$ ). Interestingly, the difference in CA 19-9 levels between the locally advanced and metastatic groups was not significant.

The area under the ROC curve was 0.892. This result suggested that changes in the CA 19-9 levels may have a direct relation to resectability (Fig. 1). When the cut-off value of CA 19-9 was accepted as 189.5 U/mL, the specificity and sensitivity were 84.6% and 82.4% respectively. On the other hand, when a value of 256.4 U/mL was used as the cut-off point, the specificity and sensitivity were 92.3% and 82.4%, respectively. Table 2 lists the sensitivity, specificity, and positive and negative predictive values of CA 19-9 levels with different cut-off levels.

The ROC curve can help to assess

**Table 1**

### Serum CA 19-9 levels of resectable, unresectable and metastatic pancreatic adenocarcinoma

Group	No. of patients	Serum CA 19-9 levels, U/mL		
		Median	Mean	SEM
Resectable	18	19.3	68.8	33.2
Unresectable (locally advanced)	15	302	380	53.3
Inoperable (metastatic)	18	500	509	129

SEM = standard error of the mean.

the usefulness of the test and to determine the most appropriate cut-off point. The point that lies closest to the upper left-hand corner of the graph is chosen as the cut-off that maximizes both sensitivity and specificity simultaneously. We chose 256.4 as an optimal cut-off point.

When we returned to the operation notes of the 18 patients with metastatic disease during the study, only 7 were found to harbour peritoneal implants or metastases visible to the naked eye that could have been identified by staging laparoscopy; 6 of these 7 patients had CA 19-9 levels over 256.4 U/mL.

## Discussion

The overall prognosis associated with carcinoma of the pancreas has not improved over the last 20 years.<sup>8</sup> The current modalities for staging are patient history and physical examination, laboratory studies, imaging techniques and surgical findings.<sup>1,2</sup> The enormous progress made in

imaging has resulted in more accurate diagnosis and staging. CT is extremely accurate in predicting unresectable disease, thereby avoiding unnecessary laparotomy. Thin-cut, contrast-enhanced CT has become the imaging study of choice for staging and evaluation. Although, CT can predict unresectability with great accuracy, this imaging study can only reliably predict resectability in 20%–90% of patients. Angiography and ERCP have been largely replaced by CT. The role of MRI in the diagnosis and staging of pancreatic cancer remains to be defined. Endoscopic ultrasonography is another imaging modality that has become much more accurate, but this method is highly operator dependent.<sup>3</sup> Despite the advances in preoperative imaging, surgery is the final diagnostic and staging tool. Laparoscopy is used primarily to detect obvious metastatic disease in the liver or on the peritoneal surfaces.<sup>3,9</sup>

The serum markers CEA, CA 19-9 and CA-125 have been disappointingly inaccurate. CA 19-9 has been found superior to CEA for diagnosing pancreatic cancer and is often considered to be the standard marker for this type of cancer.<sup>10,11</sup> CA 19-9 shows a high sensitivity and specificity for detecting recurrent and progressive disease and has been reported to predict resectability of pancreatic cancer. Forsmark and associates<sup>12</sup> demonstrated that patients with CA 19-9 levels greater than 300 U/mL have advanced tumours, and resection is rarely possible in

these cases. The main disadvantage of their study was small sample size. Recently, Schlieman and colleagues<sup>3</sup> demonstrated that among patients whose preoperative imaging studies indicated resectable pancreatic cancer, laparotomy may show that those with abnormally high serum levels of CA 19-9 may have unresectable disease. In their series of the 89 patients, 25 had locally advanced (unresectable) disease and 24 had metastatic disease. The mean adjusted CA 19-9 level was significantly lower in those with localized disease than those with locally advanced or metastatic disease. When a threshold adjusted CA 19-9 level of 150 U/mL was used, the positive predictive value for unresectable disease was 88%. On the other hand, in all these studies, arbitrary cut-off points were used. An efficient way to display and assess the predictive value of a parameter throughout a range of cut-off points is with ROC curves,<sup>7</sup> which we used in our study.

Several studies have shown that the association of elevated levels of CA 19-9 and unresectable pancreatic cancer is significantly obscured in the face of hyperbilirubinemia.<sup>3,13</sup> But in our study, there was no significant difference in bilirubin levels among groups, so we did not use adjusted CA 19-9 levels.

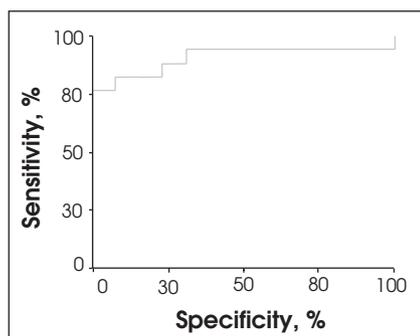
## Conclusions

The CA 19-9 level may be a useful marker for determining preoperatively which patients have unresectable pancreatic cancer. Even though it is not the main target of this study, the presence of an elevated CA 19-9 level should direct the surgeon to more liberal use of staging laparoscopy.

**Competing interests:** None declared.

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**FIG. 1.** Receiver operating characteristic curve analysis: area = 0.892, standard error = 0.62.

**Table 2**

**Sensitivity, specificity, positive and negative predictive values of CA 19-9 at different cut-off values**

CA 19-9, U/mL	Sensitivity, %	Specificity, %	PPV, %	NPV, %
28.3	94.0	69.2	75.0	92.1
47.6	88.2	69.2	69.8	85.4
77.0	88.2	76.9	79.0	86.6
128.5	82.4	76.9	78.1	81.3
189.5	82.4	84.6	84.2	82.7
256.4	82.4	92.3	91.4	83.9

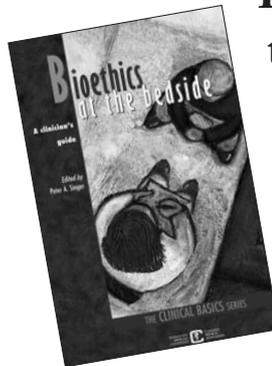
NPV = negative predictive value, PPV = positive predictive value.

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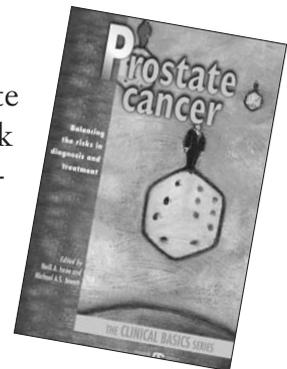
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