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CA 19–9 predicts resectability of pancreatic cancer even in jaundiced patients☆

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ABSTRACT

Background: Surgical resection remains the only curative option for pancreatic adenocarcinoma. Despite recent improvements in medical imaging, unresectability is still often discovered at the time of surgery. It is essential to identify unresectable patients preoperatively to avoid unnecessary surgery. High serum CA 19-9 levels have been suggested as a marker of unresectability but considered inaccurate in patients with hyperbilirubinemia.

Aim of the study: To evaluate CA 19-9 serum levels as a predictor of unresectability of pancreatic adenocarcinomas with a special focus on jaundiced patients.

Methods: All patients presenting with histologically-confirmed pancreatic adenocarcinoma and having serum CA 19-9 levels available prior to any treatment were included in this retrospective study. The relationship between serum concentrations of CA 19–9 and resectability was studied by regression analysis and theROC curves obtained. A cut-off value of CA 19–9 was calculated. In jaundiced patients, a CA 19–9 adjusted for bilirubinemia was also evaluated.

Results: Of the 171 patients included, 49 (29%) were deemed resectable and 122 (71%) unresectable. Altogether, 93 patients (54%) had jaundice. The area under the ROC curve for CA 19–9 as a predictor of resectability was 0.886 (95%CI:[0.832–0.932]); in jaundiced patients it was 0.880 (95% CI [0.798–0.934]. A cut-off in CA 19–9 at 178 UI/mlyielded 85% sensitivity, 81% specificity and 91% positive predictive value for resectability. There was no correlation between the levels of bilirubin and CA 19–9 ($r = 0.149$).

Conclusion: Serum CA 19–9 is a good predictive marker of unresectability of pancreatic adenocarcinoma, even in jaundiced patients. CA 19-9 levels over 178 UI/ml strongly suggest unresectable disease.

1. Introduction

Pancreatic adenocarcinoma (PA) is the fifth cause of death in France and its incidence has increased in recent years [1]. Its5-year survival rate is 5% when all stages are considered [2]. Surgical resection is the only curative treatment but the 5-year survival after resection is not higher than 20% [3]. Furthermore, only 20% of patients can undergo resection because of metastatic or locally-advanced disease at the time of diagnosis.

The main tool to evaluate the resectability of PAis CT. It evaluates resectability with sensitivity of 78–100%, specificity of 80%, a positive predictive value of 50–89%and a negative predictive value of 82–100% [4,5]. In spite of the progress in imaging, the discovery of unresectable disease is still made at surgery in nearly 25% of patients [6,7]. In addition to the morbidity of a useless laparotomy, it can delay the beginning of chemotherapy. It is therefore essential to identify unresectable disease before surgery. Moreover, these patients may benefit from either neoadjuvant or palliative treatment.

Among the tumour markers related to pancreatic cancer, the serum level of Carbohydrate Antigen 19–9 (CA 19–9) is the most used. Its value correlates with the prognosis, the TNM stage and the tumour size [8]. Several studies have shown that serum CA 19–9 is higher in unresectable patients and have suggested it as a predictor of unresectable disease when its value is very high. However, it

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carries some limits. Tumours in patients in blood group Lewis a-b-do not secrete CA 19–9 and these account for 5–10% of the population. Only 50% of pancreatic adenocarcinomas smaller than 20 mm have an increased CA 19-9 level. Finally, outside a context of PA, CA 19-9 levels may be increased in cholestatic jaundice and in acute pancreatitis. For this reason, it is classically recommended to disregard CA 19–9 in patients with jaundice, a very frequent condition at the time pancreatic head canceris discovered. In the era of evidence-based medicine there is no scientific proof to support this recommendation. The aim of this work was to assess CA 19–9 as a predictor of resectable PA with a special focus on jaundiced patients.

2. Methods

All patients with histologically-proven adenocarcinoma of the pancreatic head, body or tail and managed at our institution between January 2004 and October 2014 were included in this retrospective study if they had a CA 19-9 serum assay at the time of diagnosis (prior to any treatment). Patients with periampullary tumours other than PA (ampulloma, cholangio-carcinoma, duodenalcancer andintraductal papillary mucinous neoplasms of the pancreas) were not included and patients with hepatocellular carcinoma, colorectal carcinoma, pancreatitis, and liver cirrhosis were excluded.

2.1. Recorded data

In addition to demographic data, we recorded for each patient his/her clinical presentation, the diagnostic work-up, CA 19-9 serum concentration at diagnosis and before starting any therapy (surgery, biliary drainage, radiotherapy or chemotherapy), as well as bilirubinemia and lipasemia. Patients presenting with serum CA 19-9 lower than 5 UI/ml were defined as non-secreting and excluded from the study. The size of the neoplasm, the TNM and/or pTNM stage, the degree of differentiation of the neoplasm, its resectability and the way resectability was determined, as well as the final histological analysis in case of surgical resection were also recorded.

2.2. Definition of resectability

Tumours were defined as unresectablein cases of locally-advanced or metastatic disease. According to the definitions of the consensus statement on pancreatic cancer, we considered a tumour locally-advanced in cases of invasion of the superior mesentery artery, the common hepatic artery or the coeliac axis, as well as amore than 180° circumferential venous portal encasement or with portal thrombosis, either in the preoperative work-up or at the time of surgery [9,10]. Patients were considered metastatic in cases of histologically-proven inter-aortico-cava or lumbar lymph node metastases and, of course, if hepatic, peritoneal, pulmonary or any other histologically-proven metastases were found during the preoperative work-up or at surgery. All other tumours were deemed resectable.

2.3. Statistical analysis

The population was described using absolute and relative frequencies, means and standard deviations. A logistic regression analysis was performed to evaluate the ability of CA 19–9 to predict resectability. The area under the receiver operating characteristic (ROC) curve was calculated for patients with or without hyperbilirubinemia, as a single group and separately. The potential interactions between bilirubinemia and CA 19–9 were analysed by calculating Spearman's r correlation factor. In cases of bilirubinemia higher than 34 μmol/L (2 mg/dL), a bilirubin adjusted value of CA 19–9 was calculated by dividing serum CA 19-9 by the bilirubinemialevel as described by Schlieman et al., and also evaluated as a predictor through its respective ROC curve [11].

The sensitivity, specificity, positive and negative predictive values were calculated for every value of CA 19–9 and adjusted CA 19-9value as predictors of unresectablePA. A cut-off corresponding to the value of CA 19–9 with the best Youden index (gathering optimal sensitivity and specificity) was determined. P values lower than 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the population

One hundred and seventy-one patients met the inclusion criteria and were analysed. Demographic data, tumour locations and treatments are presented in Table 1. Among the 171 patients, a contraindication to surgery was found preoperatively in 58 of them (34%) and 64 patients had unresectable disease discovered during surgery (14 due to locally-advanced disease and 50 due to the discovery of metastases). The 49 remaining patients underwent resection with a curative intent. The flowchart regarding resectability and serum levels of CA 19–9 is presented in Fig. 1.

3.2. Serum CA 19–9 and bilirubinemia

The mean value of CA 19–9 in resected patients was 174 ± 41.7 UI/ml with a median of 77 UI/L($p < 0.001$). In patients with locally-advanced disease, the mean value of serum CA 19–9 was 986 ± 270.3 UI/ml with a median of 271UI/ml. Patients with metastatic disease (found during the preoperative work-up or at surgery) had a mean CA 19–9 of 4277 ± 975.9 UI/ml with a median of1071UI/ml. The mean CA 19-9 level was significantly lower in those with resectable disease than in those with locally-advanced (174 *vs* 986 UI/ml; $p < 0.001$) or metastatic disease (174 *vs* 4277 $p < 0.001$). The ability of CA 19–9 to predict resectability, assessed with the area under the ROC curve, was 0.886 (95% CI [0.832–0.932]) (Fig. 2). Thus, the serum CA 19-9 level accurately predicted resectability in 88.6% of patients.

Regarding bilirubinemia, 93 patients (54%) had jaundice at the time of diagnosis (bilirubinemia> 34 μmol/L) and 42 of these

Table 1
Demographic data, location of tumours and type of operation.

Characteristics	Resected n = 49	Unresected n = 122
Sex		
Male	*29 (59.2%)*	68 (55.7%)
Female	*20 (40.8%)*	54 (44.3%)
Age	*63.4 ± 12.3*	64.6 ± 13.4
Jaundice	*31 (63.3%)*	62 (50.8%)
Location of tumours		
Head	*38 (77.6%)*	78 (63.9%)
Body	*5 (10.2%)*	24 (19.7%)
Tail	*6 (12.2%)*	20 (16.4%)
Surgery		
Pancreaticoduodenectomy	*37 (75.5%)*	
Distal pancreactectomy	*9 (18.4%)*	
Central pancreatectomy	*1 (2.0%)*	
Total pancreatectomy	*2 (4.1%)*	
Biliodigestive diversion		26 (21.3%)
Gastroenteroanastomosis alone		16 (13.1%)
Exploratory laparotomy		21 (17.2%)
Exploratory laparoscopy		1 (0.8%)
No surgery		58 (47.6%)

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