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Utility of Serum CA19-9 Levels in the Diagnosis of Pancreatic Ductal Adenocarcinoma in an Endoscopic Ultrasound Referral Population

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Abstract

Purpose—Recent data suggest the use of carbohydrate antigen (CA) 19-9 as a potential marker in the early detection of pancreatic ductal adenocarcinoma (PDAC) when used in the appropriate clinical setting. Here, we assess the utility of CA19-9 in PDAC detection in a select population of pancreatic endoscopic ultrasound (EUS) referrals.

Methods—Retrospective review of an institutional EUS Pancreas Registry containing cases referred from November 2002 to November 2011 was completed for categorical analyses with CA19-9 level. A separate case-control study for the subset of non-elevated CA19-9 PDAC population was also performed to characterize the clinical features in this unique group of patients.

Results—Two hundred eighty-three patients had available CA19-9 data in the registry and were included in the study. Compared to the typical PDAC distribution, the proportion of patients with stage I disease was significantly higher in our registry population ($P < 0.0001$). Elevated CA19-9 levels most often reflected a diagnosis of PDAC relative to other pancreaticobiliary diagnoses. However, we observed that 15 % of patients with PDAC had normal CA19-9 levels. Clinical characteristics for this false-negative PDAC group compared to the true-positive group demonstrated a predilection for detection of cancer in the body/tail of the pancreas ($P = 0.03$), increased likelihood of lymph node metastases ($P = 0.03$), and initial presentation with vague abdominal pain or pancreatic mass as an incidental finding on imaging studies ($P = 0.01$).

Conclusions—Elevated CA19-9 demonstrated a greater likelihood of PDAC diagnosis relative to benign pancreatic pathology, and higher levels of CA19-9 were in line with worse PDAC stage.

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Patients with normal CA19-9 PDAC may represent a unique subclass of patients, presenting with atypical clinical features, and possibly more advanced stage disease at the time of diagnosis. These patients may benefit from more diligent EUS examination or perhaps closer follow-up management.

Keywords

Pancreatic cancer; CA19-9; Endoscopic ultrasound; Biomarker; Pancreas

Introduction

Timely diagnosis of pancreatic ductal adenocarcinoma (PDAC) remains a major challenge for practicing physicians. Most PDAC cases are diagnosed at advanced stage, and the median survival of unresectable disease ranges from 4 to 6 months with a 5-year survival rate of 6 % [1]. However, in those cases where resection is possible, the 5-year survival rate is significantly higher up to 20 % [1–4]. Early stage diagnosis, therefore, remains a critical strategy in improving the outcome of this disease.

Advances in imaging technology and laboratory techniques have led to modest improvements in this regard. Today, endoscopic ultrasound (EUS) remains the most accurate method for PDAC detection and is particularly useful in detection of lesions under 2 cm [5]. Endoscopic ultrasound offers a very high negative predictive value in tumor detection, and its use has been suggested as the standard screening method in high-risk PDAC patient groups and complementary to computed tomography and magnetic resonance imaging [6–13]. Carbohydrate antigen (CA) 19-9, an epitope of sialylated Lewis A blood group antigen, is a tumor marker initially identified in colon and pancreatic adenocarcinoma [14]. Although it is expressed in approximately 70–90 % of PDACs, the role of serum CA19-9 in aiding with diagnosis of pancreatic cancer has not been well defined [15, 16]. Owing to its poor sensitivity in early stage disease, CA19-9 has been used limitedly in early detection protocol [15–17]. Furthermore, CA19-9 can be elevated in patients with other malignancies of the gastrointestinal tract, benign diseases of the hepatobiliary system, and chronic pancreatitis [18–20]. In addition, some patients do not express the Lewis antigen, as observed in up to 10 % of the Caucasian population [21]. Therefore, the clinical utility of CA19-9 has largely remained in disease prognostication and to follow response to therapy [16, 17, 22–24].

While the utility of serum CA19-9 in screening for PDAC is limited for the general population, accumulating evidence from recent reports suggests such a role for CA19-9 when used in the appropriate subset of symptomatic patients or those at high risk for PDAC, all as part of a comprehensive diagnostic strategy [25–29]. To elaborate on this notion, we examined the utility of serum CA19-9 in a group of pancreatic EUS-referred patients, which expectedly included a larger proportion of early stage disease than the general PDAC population. In addition, we performed a case–control analysis using a unique subset of PDAC patients with non-elevated CA19-9, for its potential of early stage disease inclusion, in order to identify distinguishing clinical characteristics that may shed further light on the utility of CA19-9 in early cancer detection.

Materials and Methods

CA 19-9-based Diagnostic Category Comparison

Patients—We retrospectively reviewed the IRB-approved UC Davis EUS Pancreas Registry, which included patients undergoing EUS for investigation of pancreatic disease from November 2002 to November 2011. Patient demographic data, pre-procedure serum CA19-9 level, corresponding final diagnosis, and PDAC stages (AJCC 2010) were abstracted. CA19-9 level of 37 U/mL was used as the cutoff per manufacturer's recommendation.

Statistical Analysis—The probability of having pancreatic cancer vs another pancreaticobiliary diagnosis was modeled as a function of CA19-9 levels using logistic regression. CA19-9 values were log transformed prior to logistic regression analysis, as the range of values in the data varied over several orders of magnitude. A base-2 log transformation was used so that the odds ratio in this analysis represents the incremental change in odds of pancreatic cancer for each twofold change in CA19-9 levels.

The χ^2 test was used to compare the observed and expected distribution of patients across cancer stages. Expected distributions were determined according to data in the Surveillance Epidemiology and End Results (SEER) database [30].

Logistic regression analysis was used to compare the proportion of subjects with elevated CA19-9 levels between diagnosis categories. *P* values for pairwise comparisons of proportions between diagnosis categories were adjusted for multiple testing using the Tukey HSD method.

ROC were used to select optimal CA19-9 cutoffs for the comparison of adenocarcinoma to other diagnoses. The optimal cutoff is defined as the cutoff corresponding to the point on the ROC that is closest to the point (0,1). Confidence intervals for the optimal cutoffs were obtained via bootstrap resampling.

All analyses were conducted using R version 2.13.0 (R Development Core Team, 2011).

Case–Control Study

Patients—Among patients with diagnosis of PDAC in the registry, those with normal CA19-9 levels (<37 U/mL) were identified. We selected two control patients (PDAC with CA19-9 >37 U/mL) for every one case patient (PDAC with CA19-9 <37 U/mL). The control subjects were selected from the entire pool of PDAC patients with elevated CA19-9 to match for known disease-related and patient-related factors (age, gender, race, diabetes history, and body mass index) relative to the cases. Patient records were retrospectively reviewed, and data regarding demographic, clinical, and EUS features were analyzed.

Statistical Analysis—Fisher's exact test was used to compare categorical demographic and disease characteristics between adenocarcinoma subjects with elevated and non-elevated CA19-9 levels. A two-sample *t* test was used to compare mean age and mean BMI between adenocarcinoma subjects with elevated and non-elevated CA19-9 levels.

Results

Of the 546 patients in our database that were reviewed, 283 (52 %) had documented pre-procedure CA19-9 levels and were included in this study. Table 1 shows the patient demographics. Patients were equally distributed by gender and by age in the middle-aged to elderly groups. The majority of the study patients were Caucasian (79 %) and had a diagnosis of PDAC (52 %) by EUS. Figure 1 shows the distribution of the patients by PDAC stage. Compared to the typical PDAC stage distribution reflected by SEER data [30], the proportion of EUS PDAC Registry patients with stage I disease was significantly higher [χ^2 , 40; $P < 0.0001$], and correspondingly, the proportion of registry patients with stage IV disease was significantly lower [χ^2 , 83; $P < 0.0001$].

Among patients with elevated CA19-9 levels (> 37 U/mL), significantly more carried a diagnosis of PDAC, 73 vs 27 %, $P < 0.001$, OR 7.84 [CI 95 % (4.60–13.36)]. Logistic regression analysis found that the proportion of patients with elevated CA19-9 levels was also significantly higher in the PDAC group when compared individually to every other diagnostic category: $P < 0.001$ in comparing PDAC with benign cystic lesions, acute/chronic pancreatitis and normal pancreas, $P = 0.005$ in comparing PDAC with other pancreatic neoplasia, and $P = 0.03$ in comparing PDAC with other non-pancreatic lesions. A comparison of median CA19-9 levels across various EUS diagnoses demonstrated a significantly higher median CA19-9 level among patients with PDAC (491 U/mL) vs non-PDAC (20 U/mL), $P < 0.001$. The odds of having PDAC compared to another diagnosis increased significantly with increasing CA19-9 levels with a predicted 50.4 % increase in odds [CI 95 % (36.0–68.2 %)] associated with each twofold change in CA19-9.

The predicted probability of having PDAC vs an alternative diagnosis for a patient with a value of 37 U/mL or greater was 0.41. A CA19-9 value of 37 U/mL in our population yielded a sensitivity of 85 %, specificity of 66 %, positive predictive value of 83 %, and negative predictive value of 69 %. Receiver–operator curve (ROC) analysis selected a CA19-9 value of 88 U/mL [CI 95 % (33–158)] as the optimal cutoff for distinguishing PDAC from other diagnoses. This CA19-9 level yielded a sensitivity of 66 %, specificity of 80 %, positive predictive value of 72 %, and negative predictive value of 75 %.

The prognostic value of CA19-9 was evaluated by comparing the median CA19-9 level of different stage PDACs. There were a total of 33 patients with stage I disease, 70 patients with stage II disease, 22 patients with stage III disease, and 22 patients with stage IV disease. The median CA19-9 levels for stages I, II, III, and IV cancers were 276 (range 7–7,668), 369 (range 1–23,753), 493 (range 1–424, 589), and 2,124 (range 1–17,300) U/mL, respectively. There was a significant difference in CA19-9 level observed between stages I vs IV cancers ($P = 0.04$) and stages II vs IV cancers ($P = 0.05$). However, there was no significant difference between CA19-9 levels of stages III vs IV cancers ($P = 0.68$). There was likewise no significant difference between stages I and II cancers nor stages II and III cancers.

Among the patients with PDAC diagnosis, 127 (86 %) had elevated CA19-9 levels, while 20 (14 %) patients did not. In order to identify potential distinguishing clinical characteristics

between these two groups, we performed a case-control study consisting of 20 case patients, i.e., those with a PDAC diagnosis and non-elevated CA19-9 levels and 40 control patients, i.e., those with a PDAC diagnosis and elevated CA19-9 levels. The median CA19-9 values for the non-elevated and elevated CA19-9 groups were 9 and 1,359 U/mL, respectively. Patients were well matched for age, gender, race, BMI, and presence of diabetes (Table 2). Table 3 shows the EUS characteristics of both groups. Significantly, more cancers were localized to the body/tail compared to the head/neck/uncinate process of the pancreas among patients with normal CA19-9 levels relative to those with elevated CA19-9 levels, 45 vs 18 %, respectively, $P=0.03$, OR 3.9 [95 % CI (1.2–12.8)]. Likewise, significantly more patients with normal CA19-9 had lymph node metastases at the time of EUS, 85 vs 58 % ($P=0.03$). There was no significant difference in mass size or the detection of liver metastases ($P=0.73$). Significantly, fewer patients with normal CA19-9 levels presented with obstructive jaundice, 20 vs 51 % ($P=0.03$), and these patients were significantly more likely to have PDAC detected as an incidental finding, 20 vs 0 % ($P=0.01$) (Fig. 2). No significant difference in cancer stage was demonstrated, although there was a trend towards significantly greater stage IIB cancers among the normal CA19-9 group (60 vs 33 %, $P=0.05$) in this population.

Discussion

Timely diagnosis of PDAC has been limited by the absence of cancer-specific symptoms during early stages of disease and by lack of adequate screening methods. Much research has focused on the identification and utilization of serum tumor markers as a means to provide cost-effective PDAC screening [17]. Many such tumor markers have been identified, each with its own limitations [31]. Of these, CA19-9 has shown to be most sensitive for the detection of PDAC [32]. As recent studies have been inclined to focus on the utility of CA19-9 in EUS screening as potentially having a role in the early detection of PDAC, we set out to determine the pattern of CA19-9 levels in PDAC patients in the select setting of a tertiary care EUS referral center. Our data confirm the uniqueness of PDAC cases in EUS referral population such as ours having a significantly greater proportion of early stage/localized disease at the time of diagnosis. Consistent with other reports, our results in this subset also show an association of elevated CA19-9 levels more closely with PDAC.

Previous reports have attempted to screen for PDAC using CA19-9 with limited success [28, 29]. Most recently, Zubarik et al. proposed a CA19-9-based screening protocol in a population at high risk for PDAC [25]. An ideal screening test should not only be highly sensitive so that the disease is not missed but also have adequate specificity to avoid overdiagnosis. The sensitivity and specificity of CA19-9 for PDAC in our population at the standard cutoff value of 37 U/mL was comparable to values reported by earlier studies, 70~90 and 68~91 %, respectively [21, 33–37]. Some of these studies also demonstrated improved specificity of CA19-9 when higher cutoff values were used [33–37]. While we observed an increase in specificity of CA19-9 at the optimal cutoff of 88 U/mL for our data, the change was indeterminate as the confidence interval included the original cutoff of 37 U/mL.

The prognostic value of CA19-9 was illustrated by upward trend in CA19-9 levels with worsening cancer stage. These data echo those of others and support the role of CA19-9 in prognostication, namely higher levels correlate with later stage disease and lower median survival rates [24]. However, our results only reached significance when comparing the very extremes of the disease spectrum: early/localized cancer to late/metastatic cancer. We were unable to correlate specific cancer stages with ranges of CA19-9, so gradation of cancer stage based on CA19-9 levels was not possible.

Our data indicate that the incidence of false-negative CA19-9 PDAC cases in the EUS referral population may be as high as 15 % when a cutoff of 37 U/mL is used. Our case–control analysis revealed that patients with PDAC and normal CA19-9 levels may have a predilection for cancers in the body/tail of the pancreas, leading in turn to a more subtle presentation of vague abdominal pain rather than the classic presentation of obstructive jaundice as seen in those with elevated CA19-9. In fact, abdominal pain was the predominant presentation in our population of PDAC patients with normal CA19-9. Patients with normal CA19-9 were also more likely to have lymph node metastasis at the time of EUS evaluation, correlating with more stage IIB cancers. Together, these data suggest that patients with normal CA19-9 PDAC represent a unique subclass of patients, presenting with atypical clinical features, and possibly more advanced stage disease at the time of diagnosis. Endosonographers should be especially prudent when screening referred patients with atypical symptoms and normal CA19-9, with full examination of the body/tail of the pancreas, and assessing for locoregional lymphadenopathy. Additionally, patients with atypical symptoms and normal CA19-9 with otherwise increased clinical suspicion for PDAC may benefit from closer follow-up and serial EUS examinations so that early stage cancers are not missed.

Limitations from the retrospective review of our database restricted us to available demographic and clinical features of the patients in the study, which may not include other factors potentially affecting the level of CA19-9 such as involvement of inflammatory or excreting organ disease processes. Our database also did not have mortality data, and so it is unclear if PDAC patients with normal CA19-9 and less overt symptoms faced earlier demise. In spite of these factors, our data highlight the potential utility of pre-procedural CA19-9 in a tertiary care EUS referral population where the PDAC, and in particular early stage, are being detected at a higher proportion than in the general oncologic population. Importantly, our investigation reveals the potential distinguishing clinical and EUS characteristics of patients with PDAC and normal CA19-9 levels. Additional scrutiny of EUS referral indicators may allow identification of a greater number of clinical factors associated with early stage disease. Further search for newer and more robust tumor markers needs to continue in order to improve our early detection capability and make subsequent screening cost effective.

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Fig. 1. Distribution of EUS referral population by cancer stage. χ^2 , 40; $P < 0.0001$ for localized disease and χ^2 , 83; $P < 0.0001$ for distant metastatic disease relative to expected distribution as per SEER data

Fig. 2. Initial clinical presentation/indication for EUS referral of patients with PDAC among cases (CA19-9 <37 U/mL) and controls (CA19-9 >37 U/mL). $P=0.03$ for “jaundice” and $P=0.01$ for “incidental finding”

Table 1

Demographic features of UC Davis EUS Pancreas Registry patients with pre-procedure CA19-9

Gender	<i>N</i>
Male	139 (49 %)
Female	144 (51 %)
Age	<i>N</i>
<41	7 (3 %)
41–64	137 (48 %)
>64	139 (49 %)
Ethnicity	<i>N</i>
Caucasian	223 (79 %)
African–American	21 (7.4 %)
Hispanic	27 (9.5 %)
Asian	12 (4.1 %)
EUS Diagnosis	<i>N</i>
PDAC	148 (52 %)
Periampullary neoplasia ^a	19 (6 %)
Benign cystic lesions ^b	28 (10 %)
Acute/chronic pancreatitis	32 (11 %)
Normal	35 (12 %)
Other ^c	22 (9 %)

^aIPMN, neuroendocrine tumor, and ampullary adenocarcinoma^bBenign cyst, mucinous cystadenoma, and serous cystadenoma^cPlasma cell dyscrasias, cholangiocarcinoma, lymphoma, bile duct stone, nonspecific parapancreatic mass, pancreas divisum, benign node, metastatic lung cancer, and liver carcinoma of unknown primary

Table 2

Demographic features of case (CA19-9 <37 U/mL) and control (CA19-9 >37 U/mL) patients with PDAC

Clinical features	Cases N =20	Controls N =40	P value
Mean age	67	66	0.73
Gender			
Male	11 (55 %)	20 (50 %)	0.79
Female	9 (45 %)	20 (50 %)	0.79
Race			
Caucasian	14 (70 %)	32 (80 %)	0.52
Hispanic	3 (15 %)	3 (7.5 %)	0.39
African–American	2 (10 %)	2 (5 %)	0.59
Asian	1 (5 %)	3 (7.5 %)	1
Diabetes	8 (40 %)	13 (33 %)	0.58
Mean BMI	28	27	0.7

Table 3

Characteristics of pancreatic mass lesion on EUS among cases (CA19-9 <37 U/mL) and control (CA19-9 >37 U/mL) patients

	Cases <i>N</i> =20	Controls <i>N</i> =40	<i>P</i> value
Mass location			
Head/neck/uncinate	11 (55 %)	33 (82.5 %)	0.03
Body	4 (20 %)	3 (7.5 %)	0.42
Tail	5 (25 %)	4 (10 %)	0.14
Mean mass size (cm)			
Length	3	3.4	0.26
Width	2.9	3.2	0.73
Lymph node positivity	17 (85 %)	23 (58 %)	0.03
Liver metastases	3	5	0.73