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The Clinical Utility of CA 19-9 in Pancreatic Adenocarcinoma: Diagnostic and Prognostic Updates

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Abstract

CA 19-9 and CEA are the most commonly used biomarkers for diagnosis and management of patients with pancreatic cancer. Since the original compendium by Steinberg in 1990, numerous studies have reported the use of CA 19-9 and, to a lesser extent, CEA in the diagnosis of pancreatic cancer. Here we update an evaluation of the accuracy of CA 19-9 and CEA, and, unlike previous reviews, focus on discrimination between malignant and benign disease instead of normal controls. In 57 studies involving 3,285 pancreatic carcinoma cases, the combined sensitivity of CA 19-9 was 78.2% and in 37 studies involving 1,882 cases with benign pancreatic disease the specificity of CA 19-9 was 82.8%. From the combined analysis of studies reporting CEA, the sensitivity was 44.2% (1,324 cases) and the specificity was 84.8% (656 cases). These measurements more appropriately reflect the expected biomarker accuracy in the differential diagnosis of patients with periampullary diseases. We also present a summary of the use of CA 19-9 as a prognostic tool and evaluate CA 19-9 diagnostic and prognostic utility in a 10-year, single institution experience.

I. INTRODUCTION

CA 19-9 was first discovered in 1979 by researchers using monoclonal antibodies to isolate tumor associated antigens in colorectal carcinoma and two years later was also found to be produced by pancreatic carcinoma [1, 2]. In 1983 a radioimmunoassay was developed for measuring CA 19-9 levels [3] and it rapidly became the most well studied and used biomarker for pancreatic ductal adenocarcinoma (PDAC). CEA is likely the second most used biomarker for PDAC. Neither biomarker possesses the accuracy desirable for screening asymptomatic populations [4, 5], therefore CA 19-9 and CEA are used in conjunction with imaging for directing diagnostic and treatment decisions in patients with suspected PDAC or other periampullary disease. The identification of novel biomarkers with improved

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performance over CA 19-9 for PDAC diagnosis and monitoring has been a research priority in recent years (reviewed in [6]).

The low incidence of PDAC in the general population requires a highly accurate screening test in order to decrease the number of false positive results that would lead to expensive and possibly invasive confirmatory examinations [6]. Although it is the most widely used biomarker for PDAC, CA 19-9 has several limitations that should be considered when interpreting serum levels in the clinical setting. CA 19-9 is a sialylated Lewis (Le^{ab}) blood group antigen [1]. While the majority of people are either Le^{a+b-} or Le^{a-b+} , approximately 6% of the white population and 22% of the black population in the United States are Le^{a-b-} and do not generate the specific sialyl antigen [7-11]. CA 19-9 will be falsely negative for this portion of the population, which reduces its effectiveness as a diagnostic marker. CA 19-9 is also not specific to pancreatic cancer as it can be elevated in extra-pancreatic malignancies and benign hepatopancreaticobiliary conditions, contributing to lower diagnostic accuracy for PDAC.

CA 19-9 has been evaluated in screening asymptomatic populations for pancreatic adenocarcinoma in at least two large studies. In a Korean study [5], 70,940 asymptomatic patients were screened using an upper limit of normal for CA 19-9 at 37 U/ml, the standard clinical cut-off. Of the 1,063 cases that had elevated CA 19-9 (for a specificity of 98.5%), only 4 patients with pancreatic cancer were detected, although 11 cases with other malignancies were found. Another study screened 10,162 asymptomatic Japanese adults over the age of 40 and found 4 cases of pancreatic cancer [4]. The conclusion from both studies was that screening of asymptomatic subjects using CA 19-9 was ineffective due to the low positive predictive value. Furthermore, screening asymptomatic patients using CA 19-9 may be futile for early detection of PDAC as CA 19-9 has been shown to be ineffective in small malignant tumors of the pancreas [12]. Better results were achieved when screening was performed on patients with gastrointestinal complaints or icterus. In this outpatient study, 4506 cases were screened using CA 19-9 yielding 85 patients with pancreatic cancer [4]. This result reflects the current use of CA 19-9 for directing diagnostic decisions in patients with suspected PDAC or periampullary disease.

An initial compendium reporting the use of CA 19-9 in the diagnosis of PDAC by Steinberg in 1990 examined 24 studies involving 1,040 patients and 3,282 controls and threshold values of 37-40 U/ml [13]. The resulting mean estimates for sensitivity and specificity of 81% and 90%, respectively, are often quoted as the standard for CA 19-9 accuracy in pancreatic disease. This analysis included, as controls, healthy normal subjects and, as such, does not reflect clinical population of concern. In recent years, numerous published studies have examined novel PDAC biomarkers and have used CA 19-9 as a comparator, providing an opportunity to re-evaluate the accuracy of CA 19-9 in the largest meta-analysis to date. Similar treatment for CEA as a PDAC biomarker is lacking in the literature. Although reported in fewer studies, sufficient information was available for statistical evaluation of CEA as a PDAC biomarker. The focus of this review will be to determine the accuracy of CA 19-9 and CEA in the diagnosis of PDAC, particularly in the setting of a differential diagnosis including chronic pancreatitis. A secondary purpose of this review is to summarize what is known of the value of CA 19-9 as a prognostic tool to stratify cases of PDAC

resectable for cure, monitor treatment effectiveness, and predict survival. In this review we summarize both the available literature and add a 10-year single institution experience.

II. META-ANALYSIS: CA 19-9 AND CEA AS DIAGNOSTIC BIOMARKERS

A literature search was performed for pancreatic cancer and CA 19-9 or CEA as search terms. Those papers reporting CA 19-9 or CEA as biomarkers were further evaluated. The search was limited to English language journals. Only studies reporting biomarker levels from pretreatment samples or were clearly designated as diagnostic studies were included in the meta-analysis. Studies that included post-resection cases or malignancies other than pancreatic carcinoma were excluded from sensitivity calculations. For inclusion in the meta-analysis, the definition of pancreatic cancer included the more common pancreatic adenocarcinoma as well as pancreatic acinar cell carcinoma and pancreatic adenosquamous carcinoma. The two latter diagnoses are rare, making up less than 2% of the reported malignancies. Diagnoses of ampullary adenocarcinoma are also rare, making up about 7.4% of malignancies in our experience. In the literature reviewed, ampullary adenocarcinoma was rarely explicitly excluded from pancreatic carcinoma groupings and may have been considered in some studies included in our meta-analysis. Although patients with carcinoma arising in the ampulla have a better prognosis, treatment regimens for ampullary adenocarcinoma and pancreatic adenocarcinoma are comparable and rely on similar diagnostic decisions. Neuroendocrine tumors, which arise in the endocrine pancreas, were excluded. Studies that included healthy controls or extra-pancreatic benign disease in specificity calculations were excluded in our meta-analysis. In several cases, sensitivities and specificities other than those reported could be calculated from information in the manuscripts in order to satisfy selection criterion. CA 19-9 and CEA control data for research groups reporting sequential studies or multiple studies of different biomarkers was limited to one instance for inclusion in the meta-analysis. The *a priori* CA 19-9 upper limit of normal range requirement for inclusion in the meta-analysis was 35 – 40 U/ml. However, for the studies that met all inclusion criteria, the range was 37 – 40 U/ml with 91% (52/57) of the studies using 37 U/ml. The inclusion criterion for CEA was an upper limit of normal range of 2.5 – 5 ng/ml.

CA 19-9 data from 57 studies representing 3,285 patients with pancreatic cancer satisfied the selection criterion for inclusion in sensitivity calculations and 37 studies representing 1,882 cases with benign pancreatic disease satisfied the selection criterion for inclusion in specificity calculations (Table 1). Although not necessarily a constraint of the selection criterion, the 37 studies selected for CA 19-9 levels in benign disease represented a subset of the 57 studies selected for CA 19-9 measurement in pancreatic cancer. For the 37 studies included in CA 19-9 specificity calculations, 33 studies (89%) included chronic pancreatitis, the most common confounding diagnosis for patients presenting with a suspicion of pancreatic cancer. The remaining 4 studies specified only “benign pancreatic disease”. Acute pancreatitis cases were included in 13 studies. Five studies also listed cystic neoplasm, benign jaundice, or chronic pancreatic insufficiency. For CEA, data from 23 studies representing 1,324 patients with pancreatic cancer satisfied the selection criterion for inclusion in sensitivity calculations and 9 studies representing 301 cases with benign

pancreatic disease satisfied the selection criterion for inclusion in specificity calculations (Table 2).

Statistical analyses were performed using the “meta.summaries” function in the “rmeta” package in R version 2.8.0 [14]. The random effects method described by DerSimonian and Laird was used to model sensitivity and specificity [15]. The random effects model allows for the “true” sensitivity or specificity in a given trial to vary from some overall mean. If *m* is the total number of subjects in a trial *x* and is the observed number of true positives, then the estimated log odds (logit) sensitivity for a given trial $\hat{\eta}=ln\left(x/\left(m-x\right)\right.$ was assumed to follow a normal distribution with mean η and variance. Differences between trials were modeled as a random effect for . Specificity was treated similarly, except that it was necessary to add 0.5 to both *x* and *m*–*x* to correct for the presence of zeros in the specificity data.

Results of the meta-analysis are shown in Table 3. The summary estimates for CA 19-9 were 78.2% mean sensitivity and 82.8% mean specificity for discriminating pancreatic carcinoma from benign pancreatic disease in the included studies. This sensitivity estimate is consistent with the 81% reported in the initial compendium [13], however, the specificity of 82.8% was lower than their reported specificity of 90%. It is likely that this difference between the two studies reflects the inclusion of healthy control subjects in the prior study. The lower specificity estimate of 82.6% probably better reflects the current clinical use of CA 19-9 for discriminating malignant and benign conditions in cases presenting with periampullary disease.

CEA is the second most common serum biomarker used clinically for detecting PDAC. As shown in Table 3, the mean sensitivity and specificity estimates for CEA were 44.2% and 84.8% respectively. The sensitivity value was slightly higher than the mean sensitivity of 41% reported by Steinberg [13], who did not report a specificity for CEA. A recent compendium reported median CEA estimates for sensitivity as 54% and specificity as 79% in an analysis of 13 studies reporting CEA values in a total of 1,323 cases [16]. The decreased sensitivity and increased specificity for CEA estimates seen on our study may be explained by the differences in analytical techniques (mean vs. median estimates) and the two studies are likely comparable. The conclusion from both studies is that CEA is less accurate than CA 19-9 for identification of malignant pancreatic disease, but has similar specificity for identification of benign pancreatic conditions.

The significant results for the Chi-square tests for homogeneity of effect (Table 3) imply that the actual sensitivity and specificity of the studies are not the same (except for specificity of CEA). For the specificity calculation, this might be explained because, although the control group heavily favored chronic pancreatitis, other benign cases were included in some studies. For sensitivity calculations, the significant effects might be due to the inclusion in some studies of pancreatic malignancies other than PDAC or other subject selection criteria such as examining only early stage disease. Different choices for cutoff threshold in the various studies likely contributed to heterogeneity between the studies.

III. CA 19-9 AS PROGNOSTIC BIOMARKER FOR PDAC

In addition to being one of the most commonly utilized diagnostic biomarkers for PDAC, CA19-9 has been used to predict tumor stage and resectability, overall survival, and response to therapy in PDAC patients. Studies have shown that preoperative CA 19-9 is associated with pathologic stage and resectability of PDAC. One study demonstrated preoperative CA 19-9 correlated with pathologic stage, with median CA 19-9 values increasing with advancing stage [17]. This study also demonstrated a trend towards lower median CA 19-9 level in patients with lymph node negative disease compared to those with positive nodes (90 U/ml vs. 164 U/ml, respectively; $P = 0.06$). A study examining the predictive value of CA 19-9 for surgical resectability demonstrated lower mean CA 19-9 levels in patients with resectable PDAC compared to unresectable PDAC (68.8 U/ml vs. 622 U/ml, respectively; $P< 0.05$) [18]. Finally, a study of PDAC patients who underwent staging laparoscopy found that median preoperative CA 19-9 levels were lower in patients who underwent resection as compared to those found with unresectable disease at time of laparoscopy (131 U/ml vs. 379 U/ml, respectively; $P = 0.003$) [19]. These studies suggest that CA 19-9 levels can be utilized to predict whether a patient is a candidate for surgical resection or if distant metastases are present.

CA 19-9 levels have been shown to predict survival in PDAC patients. Lower levels of CA 19-9 prior to treatment with surgical resection or chemotherapy are associated with increased survival, especially when CA 19-9 levels are normal (<37 U/ml). One such study showed that patients with a preoperative CA 19-9 level < 37 U/ml had significantly increased survival compared to those with a CA 19-9 level elevated above 37 U/ml [20]. Another group found that CA 19-9 levels < 120 U/ml prior to surgical resection correlated with higher survival at 1, 3, and 5 years as compared to CA 19-9 > 120 U/ml in PDAC patients ($P = 0.002$) [21]. Similarly, patients with preoperative CA 19-9 < 37 U/ml had significantly better survival than those with elevated CA 19-9 levels > 400 U/ml (22 months vs. 15 months; $P=0.02$) [22]. In stage III and IV PDAC patients who underwent gemcitabine-based chemotherapy, those with pretreatment CA 19-9 levels < 37 had significantly higher survival than those with CA 19-9 levels between 38 – 1167 U/ml or CA 19-9 > 1167 U/ml (15.5 months vs. 11.9 months vs. 8. months, respectively; $P = 0.05$) [23]. These studies suggest that pretreatment CA 19-9 level is an independent prognostic marker for survival in PDAC.

A decrease in CA 19-9 levels after treatment with surgical resection has been shown to predict survival in PDAC patients. Patients with post-resection CA 19-9 < 180 U/ml had a median survival of 21 months compared to only 9 months for patients with CA 19-9 > 180 U/ml ($P < 0.0001$), regardless of the type of subsequent chemotherapy used [24]. Similar results were also noted for post-resection CA 19-9 < 90 U/ml compared with CA 19-9 > 90 U/ml (23 months vs. 10.4 months, respectively; $P < 0.001$). In another study, patients with post-resection CA 19-9 < 37 U/ml had an improved median survival of 25.6 months, compared to 20.7 months for CA 19-9 between 37 and 120 U/ml and 14.8 months for CA 19-9 < 120 U/ml ($P = 0.005$) [25]. In a study of PDAC patients with pre-resection CA 19-9 levels > 37 U/ml, those patients whose CA 19-9 levels did not decrease to a normal level (< 37 U/ml) after surgery had poorer survival than those whose CA 19-9 did return to normal

($P < 0.0001$) [26]. An increase from pre- to postoperative CA 19-9 level was also significantly associated with worse survival [20]. Therefore, in patients who undergo surgical resection for PDAC, a postoperative decrease in CA 19-9 levels is a predictive marker for improved survival.

CA 19-9 levels have also been shown to predict response to therapy, and have been used to successfully monitor the clinical course of patients and chemotherapy. Several studies have shown that CA 19-9 levels during and after chemotherapy can predict overall survival, and therefore predict a patient's response to treatment. Increased survival was observed in stage III and IV PDAC patients who underwent gemcitabine-based chemotherapy and had a decreased post-treatment CA 19-9 levels as compared with pretreatment levels. Patients who had a decrease in CA 19-9 > 89% were shown to have a median overall survival of 16.7 months, compared with 10.0 months for a decrease in CA 19-9 between 50 – 80% and 6.5 months for an increase or decrease <50% in CA 19-9 [23]. Patients with locally advanced or metastatic PDAC who underwent chemotherapy with gemcitabine and had a decrease of > 20% of baseline CA 19-9 level had a significantly better median survival after 8 weeks of treatment as compared to those with <20% decrease in CA 19-9 (268 days vs. 110 days, respectively; $P < 0.001$) [27]. Thus, a decrease from pre- to postoperative CA 19-9 levels is a predictive marker for improved survival in patients who undergo treatment with chemotherapy.

CA 19-9 levels have also been shown to correlate with the progression or remission of disease after treatment, and thereby predict the response to therapy. A study of patients undergoing neoadjuvant chemoradiation prior to surgical resection showed fewer patients with declining CA 19-9 levels after treatment had distant metastases (6 of 29 patients, or 21%) compared to those with increasing CA 19-9 levels (9 of 10 patients, or 90%) (P=0.009) [28]. A study of 87 PDAC patients undergoing treatment with gemcitabine and cisplatin found 15 patients achieved a complete or partial remission according to imaging criteria; of these individuals, 14 were considered a “CA 19-9 responder” due to a decrease in CA 19-9 of > 50% within 2 months after starting treatment [29]. Another group demonstrated that log(CA 19-9) kinetics in PDAC patients after starting treatment with chemotherapy was a significant predictor for time to tumor progression (P<0.001) [30]. Finally, the change in CA 19-9 levels over a 4 week time period (“CA 19-9 velocity”) has been shown to be related to disease progression. Patients without disease progression were shown to have a slower change in CA 19-9 over a 4 week period (1 U/ml/4 weeks) as compared to those with disease progression (131 U/ml/4-weeks) ($P < 0.001$) [31]. These studies suggest that a decrease in CA 19-9 levels during or after treatment are predictive of disease remission and whether a patient will respond to chemotherapy.

CA 19-9 is a useful serum marker to predict tumor stage and resectability, overall survival, and response to therapy in PDAC patients, in addition to its commonly utilized function as a diagnostic biomarker. Research has shown that preoperative CA 19-9 levels may correlate with disease stage and can be predictive of whether a patient is a candidate for surgical resection. CA 19-9 levels before and after surgical resection or chemotherapy are predictive of overall survival in patients, especially when there is a decrease in CA 19-9 levels after treatment. Finally, the change in CA 19-9 levels during and after chemotherapy are

predictive of a patient's response to therapy and the likelihood of disease remission. These studies are promising and demonstrate the potential CA 19-9 has for the improved management of patients with PDAC.

IV. TEN-YEAR, SINGLE INSTITUTION EXPERIENCE

For the years 2001 through 2010, 718 subjects with periampullary disease were enrolled in an Institutional Review Board-approved clinical cancer outcomes research protocol at the University of Utah Huntsman Cancer Institute. This experience offers an opportunity to examine CA 19-9 and CEA biomarker characteristics compared to the review described above. Serum CA 19-9 and CEA values, determined for clinical purposes, were abstracted from the patient records. For most patients, longitudinal measurements were available.

Of the 686 cases for which CA 19-9 measurements were available, CA 19-9 was undetectable in 55 cases (8%), which is consistent with the expected number of cases lacking the functional gene necessary to generate the CA 19-9 antigen. CA 19-9 measurements from samples collected prior to the patient receiving treatment, other than placement of a stent in jaundiced cases, were available from 600 cases (summarized in Table 4). The number of cases for each diagnoses presented in Table 4 likely represents the prevalence of each disease in patients presenting with periampullary disease at a high-volume cancer center. It is possible, however, that the PDAC cohort was skewed in ways related to referral bias in this regional center. In our sample set, CA 19-9 levels were not dispersed normally, as a relatively few case with very high levels distorted the distribution. Therefore, geometric means better reflect the central tendencies in each grouping. In general, mean values for CA 19-9 were well above the clinical cutoff of 37 U/ml for malignancies, whereas most of the benign conditions had mean CA 19-9 values below 37 U/ml. Although there was a high degree of variance in CA 19-9 values for pancreatic adenocarcinoma cases, there was a clear distinction between early stage and advanced disease with high mean CA 19-9 values in late stage, unresectable cases (Table 4).

The accuracy of CA 19-9 for discriminating malignant and benign pancreatic disease (defined in Table 4) in our patient cohort calculated using an upper limit of normal of 37 U/ml yielded sensitivity and specificity of 81.7% and 82.0%, respectively. Comparing the minimal data set of PDAC and pancreatitis yielded a sensitivity of 83.3% and a specificity of 79.2%. Receiver operating characteristic (ROC) analyses, which examine a classifier over a range of cut-off thresholds, for both comparisons are shown in Figure 1. The area under the curve (AUC) for the malignant (true positive) versus benign (true negative) pancreatic disease comparison (Figure 1A) of 0.878 indicates that there is an 87.8% probability that CA 19-9 will rank a randomly chosen true positive case higher than a randomly chosen true negative case in our cohort. CA19-9 levels had a slightly higher probability of successfully identifying a true positive from a true negative in the more restricted comparison of PDAC versus pancreatitis (Figure 1B). Although the studies used in the meta-analysis were skewed towards PDAC and chronic pancreatitis, the actual distribution of cases falls between the two comparisons used in our cohort analysis (malignant vs. benign and PDAC vs. pancreatitis). Taken together, the apparent functional sensitivity and specificity for CA 19-9 is approximately 80% each when using the conventional clinical cut-off of 37 U/ml.

However, ROC analysis of our data suggests that overall accuracy of CA 19-9 could be increased using a different upper limit of normal threshold.

In our ten year experience, pretreatment serum CEA measurements were available from 383 patients presenting with periampullary disease (Table 5). Generally, benign conditions had mean CEA levels below 5 ng/ml whereas mean levels for malignancies were above 5 ng/ml. Unlike CA 19-9, CEA appeared to better distinguish cases with chronic pancreatitis from PDAC, although the variance in PDAC cases was high indicating that many PDAC cases would have low CEA levels. Thus, high CEA levels would be informative, but low levels would not be diagnostic. Stratification of PDAC cases by CEA levels appears to also inform stage. Although localized or resectable cases had mean CEA levels above 5 ng/ml, the mean CEA levels for advanced or unresectable disease were dramatically higher.

The accuracy of CEA levels to distinguish malignant vs. benign disease in our patient cohort using a 5 ng/ml threshold was examined and yielded a sensitivity of 44.8% and a specificity of 85.0%. Limiting the analysis to comparison of PDAC and pancreatitis cases yielded a sensitivity of 47.6% and a specificity of 81.1%. These numbers are in line with the results of the CEA meta-analysis (Table 3). AUC measurements from ROC analyses (Figure 2) indicate a theoretical accuracy of around 70% for CEA in distinguishing malignant from benign disease in cases presenting with periampullary disease.

Serum CA 19-9 measurements were available for 324 PDAC cases prior to treatment of their tumor by surgical resection and/or chemoradiation therapy. Of these, 54 had CA 19-9 serum levels below 37 U/ml, while 270 had CA 19-9 levels greater than or equal to 37 U/ml. When examined in univariate Cox models, elevated CA 19-9 levels were associated with reduced survival when CA 19-9 was treated as both a continuous predictor ($P < 0.0001$) and as a discrete predictor ($P = 0.0002$, 37 U/ml cutoff). Median survival for patients with CA 19-9 levels ≥ 37 was 284 days compared with 460 days for those with CA 19-9 levels below 37 U/ml, a difference of 176 days or approximately 6 months. Our experience supports the concept that initial CA 19-9 levels at the time of diagnosis and before treatment can be used clinically to predict overall survival, regardless of whether or not the patient is ultimately treated. High initial CA 19-9 levels might be useful as a selection criteria, in conjunction with typical radiographic and clinical staging, in identifying patients who are candidates for neoadjuvant therapy prior to resection.

Finally, there is some evidence that CA 19-9 levels increase during cholestasis [32] potentially confounding diagnoses of pancreatic cancer. Others found no effect on the diagnostic sensitivity of CA 19-9 in PDAC [33]. Frena [34] found that CA 19-9 levels were increased in jaundiced patients with chronic pancreatitis and other digestive neoplasms relative to non-jaundiced patients in the same groups, but that this relationship did not occur in patients with pancreatic carcinomas. Several other studies have similarly shown a correlation between CA 19-9 and bilirubin in benign diseases but no such relationship in patients with a pancreaticobiliary malignancy [35-37]. Despite these observations, the practical implication for interpretation of CA 19-9 levels on initial presentation of patients with periampullary disease is that elevated levels of CA 19-9 in the context of jaundice does not necessarily indicate malignancy. In our experience, both CA 19-9 and total bilirubin

measurements were available from the same samples in 154 cases. CA 19-9 ranged from 1 to 304,753 U/ml and total bilirubin ranged from 0.1 to 19.6 mg/dL. A correlation z-test performed on log-transformed CA 19-9 and bilirubin values showed a modest (0.293), but significant ($P = 0.0002$) correlation indicating a relationship between elevated CA 19-9 and elevated bilirubin in our patient cohort. This analysis examined only the relationship between different patients. Further research that includes prospective longitudinal analyses in the same patient seems warranted in order to clarify the relationship between CA 19-9 and bilirubin in patients with periampullary disease.

VII. CONCLUSION

CA 19-9 is currently the gold standard serum biomarker for the diagnosis of PDAC. CA 19-9 should at a minimum possess the appropriate sensitivity and specificity necessary to accurately distinguish PDAC from benign conditions in a clinical setting. Previous reports evaluating the effectiveness of CA 19-9 and CEA included normal cases. In light of the low positive predictive value of CA 19-9 for screening asymptomatic populations, we have reevaluated the accuracy of CA 19-9 and CEA in the clinically relevant context comparing malignant and benign periampullary disease. Both our meta-analysis and our own ten year experience yielded a sensitivity of 80% and specificity of 80% for CA 19-9 (37 U/ml cutoff) and a sensitivity of 45% and specificity of 85% for CEA (5 ng/ml cutoff). Recent evidence does support the utility of CA19-9 as a potential prognostic biomarker for PDAC, especially with regards to predicting survival following clinical treatment. CEA has more limited usefulness than CA 19-9 in diagnosing PDAC, but if the cut-off of 5.0 ng/ml is used in a patient exhibiting signs and symptoms suspicious for PDAC the specificity is high enough to aid in clinical diagnosis.

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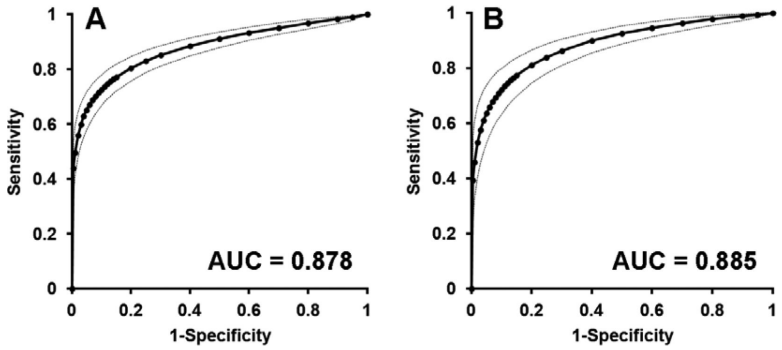

Figure 1.

Receiver-Operator Characteristics for CA 19-9. Curves demonstrate the relative accuracy for CA 19-9 in discriminating malignant (N = 355) and benign (N = 194) cases (A) or PDAC (N = 324) and pancreatitis (N = 77) cases (B) as defined in Table 4. AUC = area under curve.

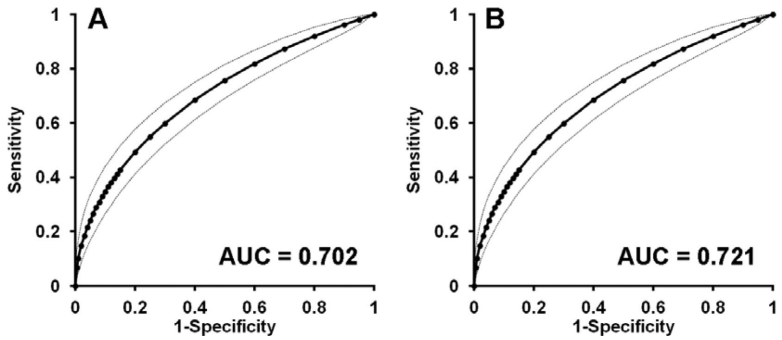

Figure 2.

Receiver-Operator Characteristics for CEA. Curves demonstrate the relative accuracy for CEA in discriminating malignant (N = 230) and benign (N = 153) cases (A) or PDAC (N = 206) and pancreatitis (N = 53) cases (B) as defined in Table 5. AUC = area under curve.

Table 1

Sensitivity and Specificity of CA19-9 in PDAC (upper reference limit of 37-40 U/ml)

Authors	PubMed ID	Malignant Cases	Sensitivity	Benign Cases	Specificity	Upper Reference Limit (U/ml)	Citation
Andriulli et al.	3940235	76	78.9%	72	90.3%	37	[38]
Aroasio and Piantino	1723534	52	76.9%	32	84.4%	40	[39]
Banfi et al.	8776607	42	85.7%	20	90.0%	37	[40]
Benini et al.	3163149	25	92.0%	-	-	37	[41]
Bloomston et al.	17003645	59	71.2%	59	83.1%	37	[42]
Cerwenka et al.	10216504	38	65.0%	-	-	37	[43]
Chang et al.	17575540	72	87.5%	39	71.8%	37	[44]
Cwik et al.	17043274	73	80.8%	37	89.2%	37	[45]
Del Favero et al.	3456255	29	69.0%	27	88.9%	37	[46]
DelMaschio et al.	1984331	54	81.5%	27	81.5%	37	[47]
Dianxu et al.	12409826	41	73.2%	-	-	37	[48]
Duraker et al.	17262731	123	81.3%	58	75.9%	37	[49]
Ehmann et al.	17312459	96	75.0%	-	-	37	[50]
Farini et al.	3859414	30	73.3%	29	96.6%	37	[51]
Firpo et al.	19082654	75	77.3%	74	83.8%	37	[52]
Gansauge et al.	8980403	77	74.0%	-	-	37	[53]
Goonetilleke et al.	17414054	76	71.0%	-	-	39	[54]
Gupta et al.	2408729	17	76.5%	-	-	39	[55]
Hayakawa et al.	2451556	40	67.5%	31	100.0%	37	[56]
Hayakawa et al.	10211418	27	77.8%	49	71.4%	37	[57]
Hedström et al.	10508123	27	70.4%	-	-	38	[58]
Heptner et al.	2814339	68	82.3%	-	-	37	[59]
Hyöty et al.	1356458	47	80.9%	38	84.2%	37	[60]
Iishi et al.	3513940	14	78.6%	48	89.6%	37	[61]
Jalanko et al.	6198342	25	76.0%	32	84.3%	37	[62]
Jansa et al.	8886824	13	76.9%	12	100.0%	37	[63]
Jiang et al.	15313690	129	83.6%	-	-	37	[64]
Joergensen et al.	19820423	51	86.0%	-	-	37	[65]
Kim et al.	10406263	90	76.7%	70	87.1%	37	[66]
Koopman et al.	16428484	50	62.0%	-	-	37	[67]
Kuusela et al.	2021550	66	75.8%	42	73.8%	37	[68]
Liao et al.	18086633	112	75.4%	38	60.6%	37	[69]
Liao et al.	19214136	58	81.0%	-	-	37	[70]
Louhimo et al.	15138364	160	86.9%	-	-	37	[71]
Malesci et al.	3465666	63	90.5%	49	89.8%	40	[72]
Matsumoto et al.	7846018	16	0.0%	-	-	37	[73]

Authors	PubMed ID	Malignant Cases	Sensitivity	Benign Cases	Specificity	Upper Reference Limit (U/ml)	Citation
Meggiato et al.	1708317	27	85.2%	25	72.0%	37	[74]
Morris-Stiff et al.	20007080	73	95.9%	115	73.0%	37	[36]
Ni et al.	15698733	105	80.0%	-	-	37	[75]
Nishida et al.	3422536	12	83.3%	-	-	37	[76]
Ozkan et al.	14571813	40	75.0%	15	80.0%	37	[77]
Pasquali et al.	3472197	37	67.6%	23	95.6%	37	[78]
Piantino et al.	3458359	99	82.8%	151	92.1%	37	[79]
Plebani et al.	8233283	34	91.2%	-	-	37	[80]
Raedle et al.	8884844	33	69.7%	52	71.2%	37	[81]
Robles-Diaz et al.	2028950	26	92.3%	26	76.9%	37	[82]
Safi et al.	9496523	347	85.3%	300	84.0%	37	[83]
Sakahara et al.	3456252	55	80.0%	22	90.9%	37	[84]
Sakamoto et al.	3471687	30	86.7%	31	93.5%	37	[85]
Satake et al.	2411125	29	75.9%	39	87.2%	37	[86]
Savarino et al.	6724164	22	72.7%	37	91.9%	37	[87]
Slesak et al.	10897004	46	69.6%	74	81.1%	37	[88]
Steinberg et al.	2416628	37	89.2%	48	83.3%	37	[89]
Tatsuta et al.	3863691	32	75.0%	19	89.5%	37	[90]
Wang et al.	3554223	24	83.3%	-	-	37	[91]
Wu et al.	16643340	39	71.8%	-	-	37	[92]
Yoshikawa et al.	2581838	27	92.5%	22	95.5%	37	[93]
		3285		1882			

Table 2

Sensitivity and Specificity of CEA in PDAC (upper reference limit of 2.5 - 5 ng/ml)

Authors	PubMed ID	Malignant Cases	Sensitivity	Benign Cases	Specificity	Upper Reference Limit (ng/ml)	Citation
Aroasio and Piantino	1723534	52	40.4%	32	93.8%	5	[39]
Cerwenka et al.	10216504	38	22.0%	-	-	5	[43]
Del Favero et al.	3456255	29	31.0%	27	85.2%	3.47	[46]
Duraker et al.	17262731	123	39.0%	58	91.4%	5	[49]
Ehmann et al.	17312459	96	56.3%	-	-	2.5	[50]
Gansauge et al.	8980403	77	49.4%	-	-	3	[53]
Gupta et al.	2408729	17	47.1%	-	-	5	[55]
Hayakawa et al.	2451556	40	27.5%	-	-	5	[56]
Heptner et al.	2814339	68	52.9%	-	-	4	[59]
Jalanko et al.	6198342	19	68.4%	26	84.6%	2.5	[62]
Kuusela et al.	2021550	66	59.1%	42	78.6%	3	[68]
Liao et al.	18086633	112	33.3%	38	93.9%	5	[69]
Louhimo et al.	15138364	160	46.3%	-	-	5	[71]
Matsumoto et al.	7846018	16	0.0%	-	-	5	[73]
Mroczko et al.	19629003	78	41.0%	-	-	4	[94]
Ni et al.	15698733	105	45.0%	-	-	5	[75]
Nishida et al.	3422536	17	58.8%	-	-	2.5	[76]
Ozkan et al.	14571813	40	47.5%	15	93.3%	5	[77]
Pleskow.et al.	2930108	61	10.2%	-	-	4	[95]
Satake et al.	2411125	27	37.0%	41	97.6%	5	[86]
Steinberg et al.	2416628	37	48.4%	-	-	5	[89]
Wang et al.	3554223	24	70.8%	-	-	2.5	[91]
Yoshikawa et al.	2581838	22	81.8%	22	86.4%	2.5	[93]
		1324		301			

Table 3

Meta-Analysis of Sensitivity and Specificity for CA 19-9 and CEA

Biomarker	Parameter	Estimate	95% Confidence Interval	Chi-square test for homogeneity of effect
CA19-9	Sensitivity	78.2%	76.1% – 80.2%	$P < 0.0001$
CA19-9	Specificity	82.8%	79.9% – 85.3%	$P < 0.0001$
CEA	Sensitivity	44.2%	38.5% – 50.0%	$P < 0.0001$
CEA	Specificity	87.5%	82.5% – 91.2%	$P = 0.29$

Table 4

Ten-year, Single Institution Experience for CA 19-9 in Periampullary Diseases

		Pre-treatment Serum CA 19-9	
	N	**Mean ± SD**	**Geom. Mean**
Ampullary adenocarcinoma	26	309 ± 422	107.1
Ampullary neuroendocrine	3	23 ± 18	14.5
Bile duct stricture	8	32 ± 22	24.8
Intraductal papillary mucinous neoplasm	54	50 ± 181	15.0
Mucinous cystic neoplasm	27	31 ± 63	15.6
Pancreatic acinar cell carcinoma	3	8 ± 3	7.4
Pancreatic adenocarcinoma	324	12,917 ± 84,783	395.4
Pancreatic adenosquamous carcinoma	2	6,463 ± 8,869	1563.6
Pancreatic neuroendocrine	48	27 ± 43	12.0
Pancreatitis	37	43 ± 72	15.5
Pseudocyst	40	176 ± 1,026	9.2
Serous cystadenoma	19	19 ±12	15.3
Simple cyst	3	29 ± 28	20.6
Solid-cystic papillary neoplasm	6	12 ± 11	8.8
Malignant[a]	355	11,848 ± 81,062	340.9
Benign[b]	194	67 ± 476	13.0
Pancreatic adenocarcinoma	324	12,917 ± 84,783	395.4
Pancreatitis/Pseudocyst	77	112 ± 740	11.8
Pancreatic adenocarcinoma[c]	321	13,035 ± 85,171	401.6
IA + IB + IIA (localized disease)	46	616 ± 1,187	142.0
IIB + III + IV (locally advanced or metastatic disease)	278	15,112 ± 91,877	477.9
IA + IB + IIA + IIB (resectable)	131	733 ± 2,215	165.3
III + IV (unresectable)	190	21,516 ± 110,006	740.6
IPMN + MCN (potentially pre-malignant)	81	43 ± 152	15.1

[a] includes ampullary adenocarcinoma, pancreatic acinar cel carcinoma, pancreatic adenocarcinoma, and pancreatic adenosquamous carcinoma; excludes neuroendocrine

[b] includes pancreatitis, pseudocyst, solid-cystic papillary neoplasm, intraductal papillary mucinous neoplasm (IPMN), serous cystadenoma, mucinous cystic neoplasm (MCN), simple cyst, bile duct stricture

[c] excludes cases without stage information

Table 5

Ten-year, Single Institution Experience for CEA in Periampullary Diseases

		Pre-treatment Serum CEA	
	N	**Mean ± SD**	**Geom. Mean**
Ampullary adenocarcinoma	17	6.8 ± 10.4	3.2
Ampullary neuroendocrine	3	3.9 ± 2.5	3.3
Bile duct stricture	8	3.5 ± 2.9	2.6
Intraductal papillary mucinous neoplasm	40	3.3 ± 3.3	2.3
Mucinous cystic neoplasm	24	2.6 ± 2.4	1.9
Pancreatic acinar cell carcinoma	4	1.9 ± 2.1	1.2
Pancreatic adenocarcinoma	206	67.6 ± 570.3	5.7
Pancreatic adenosquamous carcinoma	3	3.6 ± 3.0	2.5
Pancreatic neuroendocrine	40	4.9 ± 15.2	2.1
Pancreatitis	22	2.7 ± 2.5	1.7
Pseudocyst	31	3.1 ± 2.5	2.2
Serous cystadenoma	19	2.2 ± 1.7	1.7
Simple cyst	4	7.2 ± 10.1	3.0
Solid-cystic papillary neoplasm	5	2.1 ± 1.0	1.9
Malignant[a]	230	61.2 ± 539.9	5.3
Benign[b]	153	3.0 ± 3.0	2.1
Pancreatic adenocarcinoma	206	67.6 ± 570.3	5.7
Pancreatitis/Pseudocyst	53	2.9 ± 2.5	2.0
Pancreatic adenocarcinoma[c]	196	70.7 ± 584.6	5.0
IA + IB + IIA (localized disease)	33	18.4 ± 52.4	5.6
IIB + III + IV (locally advanced or metastatic disease)	163	81.3 ± 640.4	5.8
IA + IB + IIA + IIB (resectable)	89	10.6 ± 33.8	3.9
III + IV (unresectable)	107	120.8 ± 788.7	8.0
IPMN + MCN (potentially pre-malignant)	63	3.0 ± 3.0	2.1

[a] includes ampullary adenocarcinoma, pancreatic acinar cel carcinoma, pancreatic adenocarcinoma, and pancreatic adenosquamous carcinoma; excludes neuroendocrine

[b] includes pancreatitis, pseudocyst, solid-cystic papillary neoplasm, intraductal papillary mucinous neoplasm (IPMN), serous cystadenoma, mucinous cystic neoplasm (MCN), simple cyst, bile duct stricture

[c] excludes cases without stage information