Experimental optical imaging during pancreatic cancer interventions

Manen, L. van

Part I

Chapter 2

Elevated CEA and CA19-9 serum levels independently predict advanced pancreatic cancer at diagnosis

L. van Manen, J.V. Groen, H. Putter, A.L. Vahrmeijer,
R.J. Swijnenburg, B.A. Bonsing, J.S.D. Mieog

Biomarkers. 2020 Feb 13:1-8.

Abstract

Purpose

It is suggested that tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) could be used to predict stage of pancreatic cancer. However, optimal cut-off values for CEA and CA19-9 are still disputable. This study aimed to assess the value of CEA and CA19-9 serum levels at diagnosis of pancreatic ductal adenocarcinoma (PDAC) as predictors for advanced stage of PDAC in patients discussed at pancreatic multidisciplinary team (MDT) meetings.

Methods

Patients with PDAC discussed at MDT meetings from 2013 through 2017 were reviewed, in order to determine optimal cut-off values of both CEA and CA19-9.

Results

In total, 375 patients were included. Optimal cut-off values for predicting advanced PDAC were 7.0 ng/ml for CEA and 305.0 U/ml for CA19-9, resulting in positive predictive values of 83.3%, 73.6%, and 91.4% for CEA, CA19-9 and combined, respectively. Both tumor markers were independent predictors of advanced PDAC, demonstrated by an odds ratio of 4.21 (95%CI: 1.85-9.56; P=0.001) for CEA and 2.58 for CA19-9 (95%CI: 1.30-5.14; P=0.007).

Conclusion

CEA appears to be a more robust predictor of advanced PDAC than CA19-9. Implementing CEA and CA19-9 serum levels during MDT meetings as additional tool for establishing tumor resectability is worthwhile for tailored diagnostics.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related death.[1] Most patients present with metastatic disease, and a minority (20-25%) presents with localized disease eligible for curative-intended surgery.[2] Computed tomography (CT) is currently the predominant imaging modality for diagnosis and preoperative staging of PDAC. Additional diagnostics include Magnetic Resonance Imaging (MRI), Positron Emission Tomography, endoscopic ultrasound-guided fine needle aspiration and diagnostic laparoscopy.[3] However even with currently available predominant imaging modalities, in 12-18% of surgical explorations, a resection cannot be performed due to unexpected locally advanced disease or occult metastases. The high rate of this futile explorations, which have an associated morbidity up to 30% and a hospital mortality of 2% in open setting, highlights the importance of correct preoperative staging in PDAC.[4,5]

It is suggested that serum tumor markers could be used in clinical practice as an additional tool for screening, tumor staging, prediction of prognosis and even surveillance of treatment in several cancer types.[6-8] Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are the most studied serum biomarkers for establishing both diagnosis and prognosis in pancreatic cancer patients.[9,10] The role of CEA and CA19-9 in predicting advanced PDAC, defined here as either metastatic or locally advanced PDAC, has scarcely been studied and only performed in patients undergoing surgical exploration.[11,12] To our knowledge, no reports are available about the role of CEA and CA19-9 in preoperative multidisciplinary decision making.

We hypothesized that CEA and CA19-9 serum levels at diagnosis are valuable tools for the prediction of advanced PDAC. This study aimed to assess the value of CEA and CA19-9 serum levels at diagnosis as predictors for advanced PDAC in patients discussed at the pancreatic multidisciplinary team (MDT) meetings in a tertiary referral center.

Patients and Methods

Patient selection

Four hundred twenty consecutive patients with PDAC were discussed at the pancreatic MDT meetings from January 2013 through December 2017 at the Leiden University Medical Center, a tertiary referral center for pancreatic cancer patients, were retrospectively reviewed. Patients with diagnoses other than primary PDAC were excluded from the analyses. The diagnosis of PDAC was confirmed either after analysing of tumor tissue acquired during endoscopic ultrasound-guided fine needle aspiration, endoscopic retrograde cholangiopancreatography, direct biopsy of a target lesion, the resected specimen or in case there was no suspicion of another pathology on preoperative imaging. Forty-five patients with resectable disease, who did not want to undergo surgery or were unfit for surgery (as decided by the MDT) were excluded from the analyses, because resectability could not be proven by surgical exploration. One hundred sixty-one patients were excluded from analyses involving CEA and CA19-9 serum levels (Figure 1). Approval of the local Medical Research and Ethical Committee was obtained for this retrospective cohort study.

Definitions

Laboratory findings (CEA, CA19-9, and total bilirubin) were defined as the last measured value before a MDT meeting. At MDT meetings at least one medical specialist of the following departments were present: Medical Oncology, Radiology, Hepatopancreaticobiliary Surgery, Gastroenterology and Pathology. All patients underwent CT or MRI scanning in order to assess the resectability of the tumor. Tumor size was determined as the largest diameter in the transversal direction on preoperative CT or MRI. Preoperative staging of PDAC was performed according to the American Joint Committee on Cancer (AJCC; 7th edition).[13] Advanced PDAC was defined as either locally advanced pancreatic cancer (LAPC) or presence of distant metastases (M+). According to the guidelines of the Dutch Pancreatic Cancer Group (DPCG, 2012), the following criteria were applicable for LAPC:

(1) Tumor abutment of the superior mesenteric artery, celiac axis or common hepatic artery >90° of the circumference of the vessel wall.

(2) Tumor involvement of the superior mesenteric vein/portal vein vessel wall resulting in occlusion or > 270° contact.

Overall survival was calculated from the date of the first suspicion of pancreatic cancer on CT or MRI to the date of death (event) or last follow-up (censored).

Statistical analysis

First, patient- and tumor characteristics were compared between the preoperatively advanced PDAC group (determined during MDT meetings), the intraoperatively advanced PDAC group (determined during explorative surgery) and the resected group (underwent resection). Continuous variables are presented as mean (standard deviation [SD]) in normal distributed data or median (interquartile range [IQR]) in non-normal distributed data. Categorical variables are presented as absolute numbers and percentages. Chi Squared test, One-Way ANOVA, and Kruskal-Wallis test were used to compare the patients -and tumor characteristics. A Kaplan-Meier curve was used to determine the median survival. Second, the predictive value of CEA and CA19-9 serum levels at diagnosis for advanced PDAC was evaluated by comparing the advanced PDAC group (preoperatively and intraoperatively) with the resected group. Subgroup analyses were performed to investigate if serum CEA and CA19-9 levels can differentiate between patients with LAPC, M+ or both (LAPC & M+). Receiver-operating characteristic (ROC) curve analyses and the Youden-Index were used to determine the optimal cut-off values for CEA and CA19-9, after which the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the cut-off values. Lastly, a multivariable logistic regression analysis using clinically relevant parameters and the optimal cut-off values, was carried out to assess the independence of CEA and CA19-9 as predictors of advanced PDAC. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). A P-value below 0.05 (two-sided) was considered as statistically significant.

Results

Patient characteristics

Patient and tumor characteristics are summarized in Table 1. Out of the included 375 PDAC patients, 151 (40%) patients underwent resection, 68 (18%) patients were intraoperatively classified as advanced PDAC and 156 (42%) patients were classified as preoperatively advanced PDAC. The mean (SD) tumor size differed significantly (P<0.001) between the groups: 28.3 (12.8) mm in the resected group, 37.8 (17.5) mm in the intraoperative advanced PDAC group and 40.3 (17.5) mm in the preoperative advanced PDAC group. Overall survival differed significantly (P<0.001) between the three patient groups: median (95% CI) survival was 4.0 (3.3-4.8) months in the preoperative advanced PDAC group, 6.0 (4.5-7.5) months in the intraoperative advanced PDAC group and 20 (16.8-23.2) months in the resected group. The median (IQR) CEA serum level differed significantly (P<0.001) between the groups with the lowest level in the resected PDAC group (3.2; 2.0-4.8) compared to the intraoperative advanced (6.1; 3.2-21.7) and preoperative advanced PDAC group (5.1; 2.6-12.4). The median (IQR) CA19-9 serum level also differed significantly (P<0.001) between the resected group (153.0; 30.5-520.8), intraoperative advanced PDAC group (260.1; 71.3-819.7) and preoperative advanced PDAC group (458.0; 107.4-1948.0).

Determination of optimal cut-off value of CEA and CA19-9

No significant difference in CEA and CA19-9 serum levels were detected between the LAPC, M+ and LAPC & M+ group (CEA: P=0.562; CA19-9: P=0.177). Median (IQR) CEA and CA19-9 levels were 5.2 (2.7-12.0) and 367.1 (79.6-1149.0) for the LAPC group, 6.0 (3.2-24.7) and 320.4 (128.8-1215.0) for the M+ group and 5.6 (2.6-14.6) and 528.0 (180.0-3033.0) for LAPC & M+ group. Serum CEA and CA19-9 levels differed significantly between the resected and advanced PDAC patients, with an Area Under the Curve of 0.66 (95% CI: 0.59-0.74; P<0.001) for CEA and 0.68 (95% CI: 0.60-0.75; P<0.001) for CA19-9 (Figure 2). The optimal cut-off value, calculated using the Youden-Index, was 7.0 ng/ml for CEA and 305.0 U/ml for CA19-9. A CEA>7.0 ng/ml had a PPV of 83.3% and a CA19-9>305.0 U/ml had a PPV of 73.6% for presence of advanced PDAC (Table 2). The distribution of CEA and CA19-9 serum levels at diagnosis and the percentages of patients above and under the optimal cut-off values are illustrated in a boxplot (Figure 3). Diagnostic accuracy was calculated for other clinically relevant cut-off values for CEA and CA19-9 (Table S1). Furthermore, optimal cut-off values for CEA and CA19-9 serum levels were applied in the subgroups (LAPC, M+ and combined), of which the distribution per group is depicted in Figure S1.

Combined value of CEA and CA19-9 levels

Combining both optimal cut-off values yielded a 91.4% PPV for prediction of advanced PDAC (Table 2). Resection rates in the four groups were 7.9% (both elevated), 29.6% (solely elevated CEA), 36.8% (solely elevated CA19-9), and 62.0% (both not elevated). Other relevant combinations of cut-off values for CEA and CA19-9 are added in Table S1.

Multivariable analysis of predictive factors

At multivariable analysis, elevated CEA and CA19-9, female sex, age, tumor size increment were independent predictive factors for advanced PDAC (Table 3). CEA>7.0 ng/ml showed a higher odds ratio (OR) (OR: 4.18; 95% CI: 1.83-9.56; P=0.001) than CA19-9> 305.0 U/ml (OR: 2.66; 95%CI: 1.33-5.33; P=0.006).

Discussion

The aim of this study was to evaluate the value of CEA and CA19-9 serum levels in predicting advanced PDAC in patients discussed at MDT meetings. Median CEA and CA19-9 differed significantly between the resected, intraoperative advanced PDAC and preoperative advanced PDAC patient groups (P<0.001). The optimal cut-off values for predicting advanced PDAC were 7.0 ng/ml for CEA and 305.0 U/ml for CA19-9, resulting in a positive predictive value of 83.3%, 73.6%, and 91.4% for elevated CEA, CA19-9 and combined, respectively. Both tumor markers were independent predictors of advanced PDAC, however the numerical difference between CEA (OR: 4.18) and CA19-9 (OR: 2.66) could indicate that CEA appears to be a more robust factor.

Previous studies showed optimal cut-off values of CA19-9 varying between 92.77 U/ml and 353.15 U/ml, resulting in PPV varying from 79% to 95% for advanced PDAC during staging laparoscopy or laparotomy as recently reviewed by De Rosa et al.[11] Hartwig et al. reported the predictive value for resectability and survival of CA19-9 levels in 1543 patients.[14] They reported resection rates below 70% in case of preoperative CA19-9 levels >500 U/ml, which is therefore included in the definition of borderline resectable PDAC as a biological factor.[15]

Schlieman et al. valuated the role of CEA as a predictor of resectability and found no significant difference in preoperative CEA levels between the resected and non-resected group.[16] Most studies used a combination of CEA and CA19-9 levels to determine the prognosis [17-22], however, two studies evaluated a combination of those two tumor markers for prediction of resectability. [12,23] Fujioka et al. combined CEA and CA19-9 levels, yielding a NPV for resectability of 88% in 244 patients by using 5.5 ng/ml as optimal cut-off value for CEA and 157 U/ml for CA19-9.[12] Remarkably, CA19-9 was only associated with presence of metastases (both liver and peritoneal) and not significantly associated with LAPC, whereas CEA was associated with LAPC and presence of liver metastases. However, no comparison was made between median CEA and CA19-9 serum levels in LAPC and the metastasized patient group. Kim et al. demonstrated a 86.6% NPV for resectability after combining optimal cut-off values for CEA (2.47 ng/ml) and CA19-9 (92.77 U/ml) levels.[23] The large variety of optimal cut-off values could be explained by the difference in definition of (ir)resectability, the racial diversity and size of the study population. Our study included all patients discussed at MDT-meetings, which makes comparison with current literature somewhat complicated; but is clinically more relevant. Nevertheless, our cut-off values for CEA and CA19-9 were substantially higher, resulting in much higher prediction values and lower resection rates.

This study has several limitations. The tumor markers CEA and CA19-9 were not measured in all patients. In patients who did not undergo surgical exploration CEA and CA19-9 levels were less often measured. In addition, our study included all PDAC patients discussed at MDT meetings, were other studies included solely patient who underwent surgical exploration, which states the need for external validation of the optimal cut-off values in a prospective cohort study. Sixty percent of the patients discussed at our MDT meetings, underwent surgical exploration, which is significantly higher than the national average (27%).[24] This could be explained by the fact that our hospital is a tertiary referral center; patients diagnosed in other centers, who do not want further diagnostics or treatment are simply not referred to our center.

It has been shown that biliary obstruction could disturb the CA19-9 serum levels, however, after correction for biliary serum levels, CA19-9 remained an independent predictor. Another factor influencing the CA19-9 level, is the absence of a Lewis antigen, which is the case in approximately 4-7% of the population.[25,26] CA19-9 is not expressed in patients missing the Lewis antigen, even in the presence of tumors. Although we did not asses the Lewis antigen in our study, it exemplifies that CA19-9 serum levels should always be interpreted with caution. Moreover, CA19-9 is also associated with many other cancers, such as gastric or colorectal cancer.[27,28] We hypothesized that CEA is associated with tumor size because CEA is shedded into blood from tumor cells. However, in this study an increased CEA remains an independent predictor of advanced PDAC, even after correction for tumor size. Although, CEA serum levels can also be increased in colorectal cancer or metastases, lung cancer or metastases, and nicotine abuses, which illustrates its non-specificity for pancreatic tumors.[29]

Besides CEA and CA19-9, several other promising serum markers for PDAC have been reported the last years. Most studies focused on the capability of tumor marker to detect PDAC and therefore its potential for screening purposes.[30-32] For instance, carbohydrate antigen variants, such as CA242, showed good potential for early pancreatic cancer detection.[33] Moreover, it was shown that another variant, CA125, had superior detection rates for irresectable disease in a cohort of 212 patients[34], although its application is limited because a substantial proportion of patients with pancreatitis and jaundice also have increased serum CA125 levels.[32] During last years, more research is spent on microRNA detection in serum and exosomes in order to detect pancreatic tumors in early stage with promising results and high diagnostic accuracies.[35,36] Further studies should be performed to evaluate the most sensitive microRNA markers and role of these markers in prediction of advanced stage, i.e. irresectable, pancreatic cancer.

Clinical implications of our findings might be that specific patient groups need an intensified diagnostic multi-modality approach. In general, increased CEA and CA19-9 levels resulted in a high chance (91.4% PPV) of having advanced PDAC. Subgroup analysis showed that CEA and CA19-9 levels did not differ significantly between the LAPC, M+ and LAPC & M+ groups. This indicates that patients with increased CEA and CA19-9 levels should undergo meticulous preoperative staging focusing on both locoregional status and detection of distant metastases (Figure S1). MRI for example, could be used for preoperative detection of small (liver) metastases as it is more sensitive than CT, which is most commonly used.[37-40] Furthermore, diverse combinations of cut-off values and corresponding chances on having advanced disease are calculated based on our cohort, which could guide the MDT in the treatment process (Table S1). Although, it does not implicate that in case of elevated CEA and CA19-9 levels the MDT should not consider surgical treatment. In this situation we recommend a staging or diagnostic laparoscopy before performing laparotomy, which is cost-effective and therefore the current standard of care in our and some other centers.[41,42] Moreover, additional intraoperative imaging modalities (e.g. laparoscopic ultrasound or near-infrared fluorescence imaging) should also be considered in this patient category. Preliminary results showed that CEA-targeting near-infrared fluorescence imaging is promising for intraoperative evaluation of locoregional status and detection of distant metastases and further studies defining clinical benefit are ongoing.[43,44]

Conclusion

The results of this study showed that CEA and CA19-9 are independent prediction factors for presence of advanced PDAC at diagnosis. Although CEA appears to be a more robust factor for prediction of advanced PDAC in our study, combining CEA and CA19-9 cut-off values enhances the positive predictive value, which indicates that implementing these levels during MDT meetings could be worthwhile for tailored diagnostics.

Figure 1. Study flow chart of patient inclusion. *Abbreviations: CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PDAC: pancreatic ductal adenocarcinoma.*

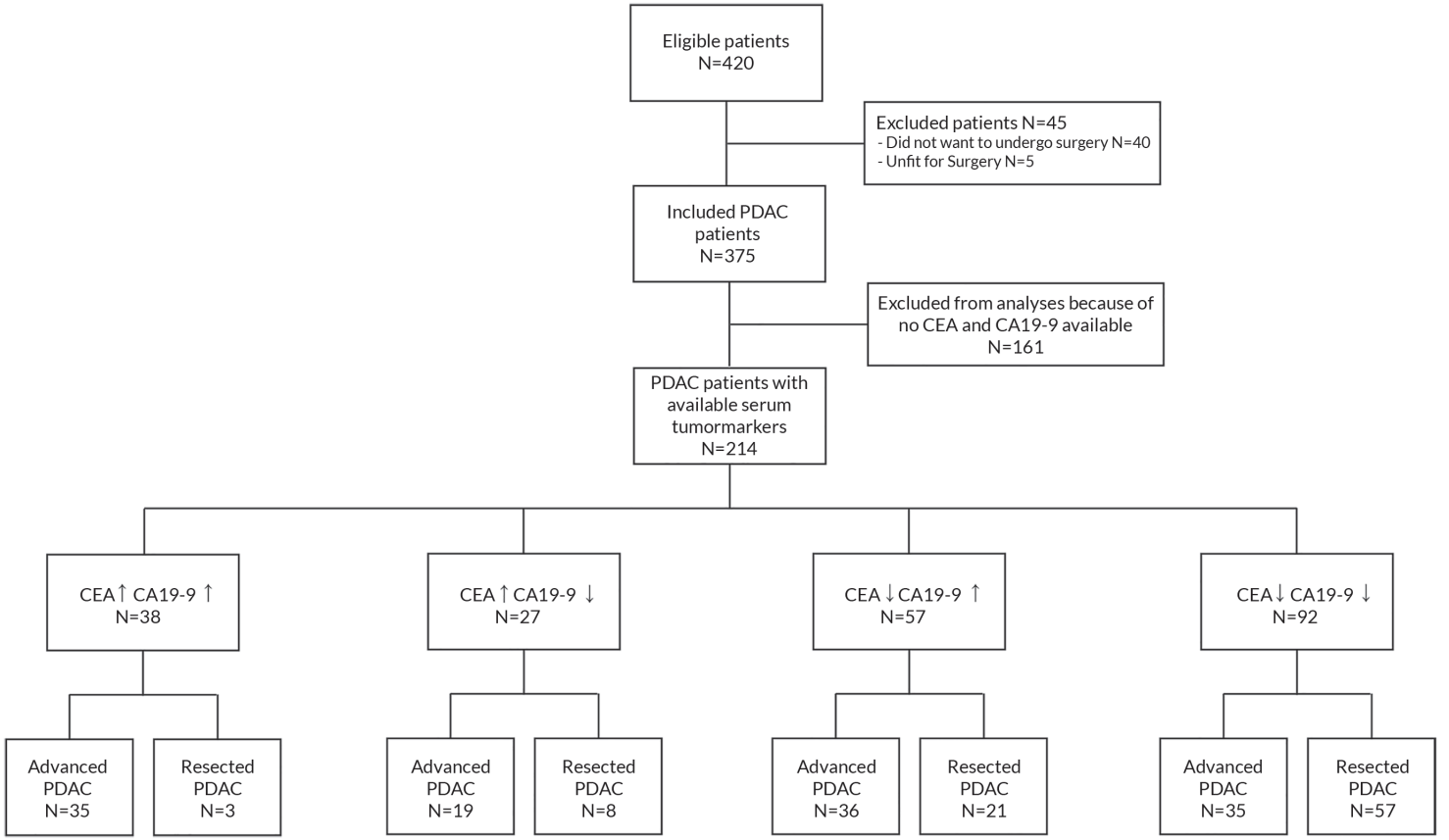


Table 1. Patient and tumor characteristics of patients discussed at the multidisciplinary team meetings.

	Resected (N=151)	Intraoperative advanced PDAC (N=68)	Preoperative advanced PDAC (N=156)	P
Age (y), *mean (SD)*	64.8 (9.6)	66.2 (9.6)	67.9 (9.8)	0.019
Sex, n (%)				0.328
Male	80 (53.0)	31 (45.6)	88 (56.1)	
Female	71 (47.0)	37 (54.4)	68 (43.6)	
ASA score, *n (%)*				0.374
1	21 (13.9)	8 (11.8)	33 (21.2)	
2	99 (65.6)	44 (64.7)	90 (57.7)	
≥3	31 (20.5)	16 (23.6)	33 (21.1)	
Bilirubin (µmol/L), *mean (SD)*	114.9 (129.8)	89.1 (120.2)	88.5 (130.5)	0.165
Tumor location, *n (%)*				0.088
Head	119 (78.8)	49 (72.1)	101 (64.7)	
Body	17 (11.3)	11 (16.2)	34 (21.8)	
Tail	15 (9.9)	8 (11.8)	21 (13.5)	
Tumor size (mm), *mean (SD)*	28.3 (12.8)	37.8 (17.5)	40.3 (17.5)	<0.001
Preoperative tumor stadium, *n* (%)				<0.001
Ia	23 (15.2)	4 (5.9)	0	
Ib	34 (22.5)	7 (10.3)	0	
IIa	75 (49.7)	34 (50.0)	9 (5.8)	
IIb	18 (11.9)	11 (16.2)	3 (1.9)	
III	1 (0.7)	9 (13.2) [1]	56 (35.9)	
IV	0	3 (4.4) [1]	88 (56.4)	
Diagnostic laparoscopy before surgery, *n* (%)	53 (35.1)	32 (47.1)	-	0.093
Reason why no resection, *n* (%)[2]				0.193
Locally advanced	-	27 (39.7)	77 (49.4)	
Involvement SMA	-	12	55	
Involvement CA	-	4	33	
Involvement CHA	-	11	61	
Involvement SMV/PV	-	21	114	
Other[3]	-	12	35	
Metastases	-	41 (60.3)	79 (50.6)	
Lung	-	0	14	
Liver	-	27	61	
Peritoneum	-	14	14	
Lymph nodes	-	8	31	
Other	-	1	3	
Median survival *(months, 95%CI)*	20.0 (16.8-23.2)	6.0 (4.5-7.5)	4.0 (3.3-4.8)	<0.001
Tumormarkers available, *n* (%)				
CEA	90 (59.6)	48 (70.6)	79 (50.6)	0.018
CA19-9	121 (80.1)	59 (86.8)	121 (77.6)	0.282
Tumormarkers, *median (IQR)*				
CEA (ng/ml)	3.2 (2.0-4.8)	6.1 (3.2-21.7)	5.1 (2.6-12.4)	<0.001
CA19-9 (U/ml)	153.0 (30.5-520.8)	260.1 (71.3-819.7)	458.0 (107.4-1948.0)	<0.001

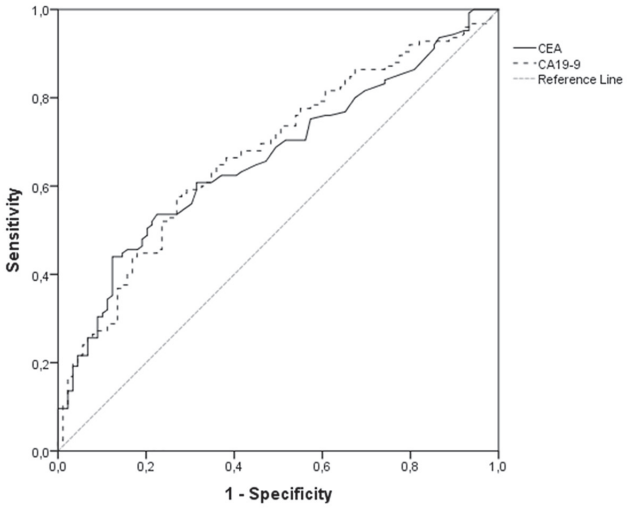
PDAC: pancreatic ductal adenocarcinoma; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; SMA: superior mesenterial artery; CA: coeliac axis; CHA: common hepatic artery; SMV: superior mesenterial vein; PV: portal vein.

[1] These patients have advanced PDAC established by preoperative imaging, however they underwent either diagnostic laparoscopy for study inclusion or intentionally palliative bypass surgery.

[2] In general, more than one structures were involved in case of locally advanced and metastatic disease. In addition, if both metastases and locally advanced PDAC was found, we considered metastases as the reason of irresectability.

[3] Local ingrowth in other structures, such as duodenum, stomach, adrenal glands, inferior caval vein and aorta.

Figure 2. ROC curves CEA & CA19-9 for prediction of advanced PDAC. *Abbreviations: ROC: receiver operating characteristic; PDAC: pancreatic ductal adenocarcinoma; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; AUC: area under the curve.*



	AUC (95%CI)	Optimal cut-off value	Youden-Index	P
CEA	0.66 (0.59 - 0.74)	7.0	0.316	<0.001
CA19-9	0.68 (0.60 - 0.75)	305.0	0.306	<0.001

Figure 3. Boxplot presentation of the distribution of CEA & CA19-9 serum levels at diagnosis. Optimal cut-off values found by ROC analysis are illustrated as a horizontal dotted line. A logarithmic scale was used on the y-axis. The percentages indicate the proportion of patients per group above and below the optimal cut-off values. *Abbreviations: CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PDAC: pancreatic ductal adenocarcinoma.*

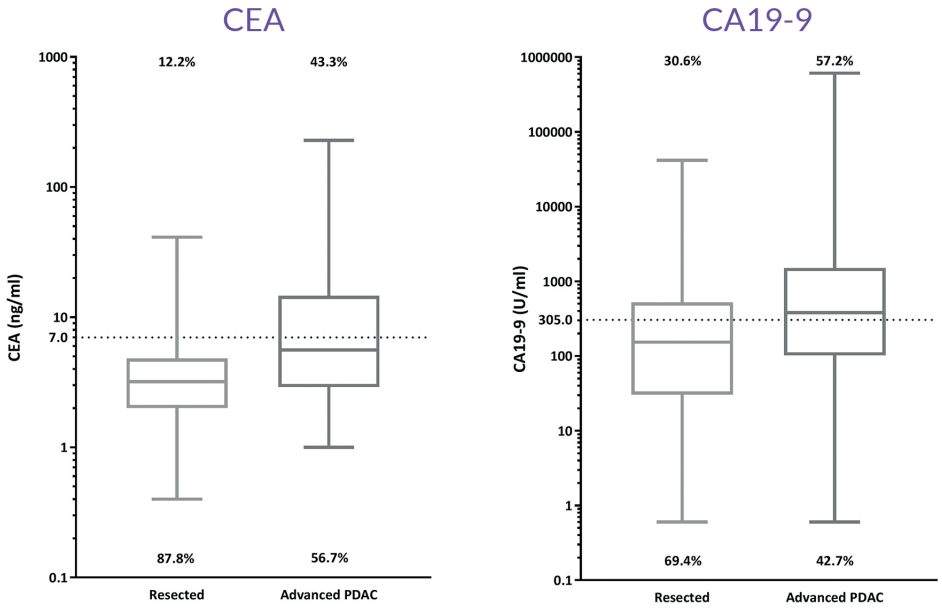


Table 2. Diagnostic value of optimal cut-off value of CEA and CA19-9 at diagnosis.

	CEA>7.0 (ng/ml)	CA19-9>305.0 (U/ml)	CEA >7.0 (ng/ml) and CA19-9>305.0 (U/ml)
Sensitivity (95% CI), (%)	43.3 (34.6 - 52.4)	57.2 (49.7 - 64.6)	27.1 (19.3 – 36.1)
Specificity (95% CI), (%)	87.8 (79.2 - 93.7)	69.4 (60.4 - 77.5)	96.4 (89.9 – 99.3)
PPV (95% CI), (%)	83.3 (73.5 - 90.0)	73.6 (67.4 - 78.9)	91.4 (77.2 – 97.1)
NPV (95% CI), (%)	52.3 (48.1 – 56.5)	52.2 (47.0 - 57.3)	48.5 (45.6 – 62.9)

CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PPV: positive predictive value; NPV: negative predictive value.

Table 3. Multivariable analysis of predictive factors for establishing advanced PDAC.

	Odds ratio	95% confidence interval	P
CEA>7.0 (ng/ml)	4.18	1.83 - 9.56	0.001
CA19-9>305.0 (U/ml)	2.66	1.33 - 5.33	0.006
Bilirubin> 17 (μmol/L)	0.61	0.30 - 1.22	0.159
Age	1.05	1.01 - 1.09	0.013
Female	2.15	1.08 - 4.30	0.029
Tumor size (mm)	1.07	1.04 - 1.10	<0.001

PDAC: pancreatic ductal adenocarcinoma; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Supplementary data

Figure S1. Boxplot presentation of the distribution of CEA & CA19-9 serum levels at diagnosis in patients with metastasized and/or locally advanced PDAC. Optimal cut-off values found by ROC analysis are illustrated as a horizontal dotted line. A logarithmic scale was used on the y-axis. The percentages indicate the proportion of patients per group above and below the optimal cut-off values. *Abbreviations: PDAC: pancreatic ductal adenocarcinoma; LAPC: locally advanced pancreatic cancer; M+: metastasized pancreatic cancer.*

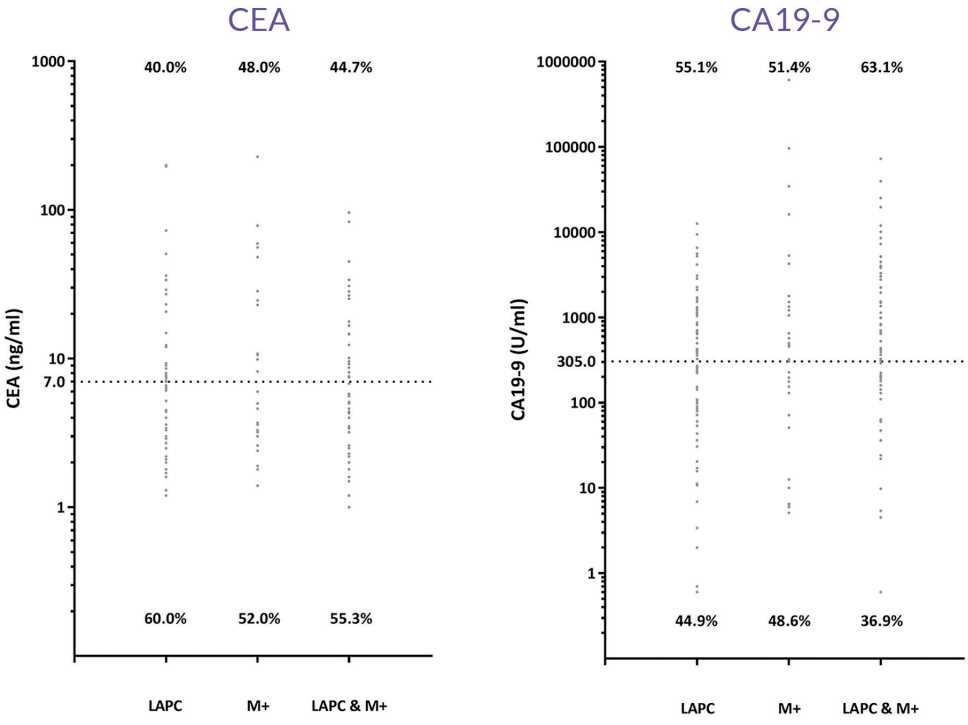


Table S1. Distribution of clinical test characteristics for different cut-off values for CEA and CA19-9.

		Number of patients (% of total)	Patients who underwent resection (resection rate [%])	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CEA (N=217)	>3.0	139 (64.1)	50 (36.0)	70.1	44.4	64.0	51.3
	>5.0	85 (39.2)	19 (22.3)	52.0	78.9	77.6	53.8
	>7.0	***66 (30.4)***	***11 (16.7)***	***43.3***	***87.8***	***83.3***	***52.3***
	>10.0	47 (21.7)	8 (17.0)	30.7	91.1	83.0	48.2
	>15.0	35 (16.1)	6 (17.1)	22.8	93.3	82.9	46.2
	>20.0	31 (14.3)	4 (12.9)	21.3	95.6	87.1	46.2
	>25.0	26 (12.0)	3 (11.5)	18.1	96.7	88.5	45.6
	>30.0	20 (9.2)	3 (15.0)	13.4	96.7	85.0	44.2
	>50.0	10 (4.6)	0 (0.0)	7.9	100.0	100.0	43.5
CA19-9 (N=301)	>30.0	247 (82.1)	91 (36.8)	86.7	24.8	63.2	55.6
	>150.0	188 (62.5)	61 (32.4)	70.6	49.6	67.6	53.1
	>305.0	***140 (46.5)***	***37 (26.4)***	***57.2***	***69.4***	***73.6***	***52.2***
	>500.0	108 (35.9)	31 (28.7)	42.8	74.4	71.3	46.4
	>600.0	100 (33.2)	26 (26.0)	41.1	78.5	74.0	47.3
	>750.0	90 (29.9)	24 (26.7)	36.7	80.2	73.3	46.0
	>1000.0	78 (25.9)	19 (24.4)	32.8	84.3	75.6	45.7
	>2000.0	48 (15.9)	10 (20.8)	21.0	91.7	79.2	43.9
	>5000.0	23 (7.6)	3 (13.0)	11.1	97.5	87.0	42.5
	>10,000.0	13 (4.3)	2 (15.4)	6.1	98.4	84.6	41.3
Combined CEA and CA19-9 (N=214)	CEA >3.0 & CA19-9 >30.0	111 (51.9)	37 (33.3)	59.2	58.4	66.7	50.5
	CEA >5.0 & CA19-9 >150.0	57 (26.6)	11 (19.3)	36.8	87.6	80.7	49.7
	CEA >7.0 & CA19-9 >305.0	***38 (17.8)***	***3 (7.9)***	***28.0***	***96.6***	***92.1***	***48.9***
	CEA >10.0 & CA19-9 >500.0	21 (9.8)	2 (9.5)	15.2	97.8	90.5	45.1
	CEA >15.0 & CA19-9 >600.0	17 (7.9)	1 (5.9)	12.8	98.9	94.1	44.7
	CEA >20.0 & CA19-9 >750.0	14 (6.5)	1 (7.1)	10.4	98.9	92.9	44.0
	CEA >25.0 & CA19-9 >1000.0	11 (5.1)	0 (0.0)	8.8	100.0	100.0	43.8

CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; PPV: positive predictive value; NPV: negative predictive value.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians. 2017;67(1):7-30.
2. Alexakis N, Gomatos IP, Sbarounis S, et al. High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015;41(2):265-269.
3. Best LM, Rawji V, Pereira SP, Davidson BR, Gurusamy KS. Imaging modalities for characterising focal pancreatic lesions. The Cochrane database of systematic reviews. 2017;4:Cd010213.
4. Kim R, Prithviraj G, Kothari N, et al. PET/CT Fusion Scan Prevents Futile Laparotomy in Early Stage Pancreatic Cancer. Clin Nucl Med. 2015;40(11):e501-505.
5. Zamboni GA, Kruskal JB, Vollmer CM, Baptista J, Callery MP, Raptopoulos VD. Pancreatic adenocarcinoma: value of multidetector CT angiography in preoperative evaluation. Radiology. 2007;245(3):770-778.
6. Adamo MP, Boten JA, Coyle LM, et al. Validation of prostate-specific antigen laboratory values recorded in Surveillance, Epidemiology, and End Results registries. Cancer. 2017;123(4):697-703.
7. Lin JX, Wang W, Lin JP, et al. Preoperative Tumor Markers Independently Predict Survival in Stage III Gastric Cancer Patients: Should We Include Tumor Markers in AJCC Staging? Annals of surgical oncology. 2018.
8. Zhang Z, Yu Y, Xu F, et al. Combining multiple serum tumor markers improves detection of stage I epithelial ovarian cancer. Gynecologic oncology. 2007;107(3):526-531.
9. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2007;33(3):266-270.
10. Meng Q, Shi S, Liang C, et al. Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis. OncoTargets and therapy. 2017;10:4591-4598.
11. De Rosa A, Cameron IC, Gomez D. Indications for staging laparoscopy in pancreatic cancer. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2016;18(1):13-20.
12. Fujioka S, Misawa T, Okamoto T, et al. Preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the evaluation of curability and resectability in patients with pancreatic adenocarcinoma. Journal of hepato-biliary-pancreatic surgery. 2007;14(6):539-544.
13. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology. 2010;17(6):1471-1474.
14. Hartwig W, Strobel O, Hinz U, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. Annals of surgical oncology. 2013;20(7):2188-2196.
15. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]. 2018;18(1):2-11.
16. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in determining resectability of pancreatic cancer. Archives of surgery (Chicago, Ill : 1960). 2003;138(9):951-955; discussion 955-956.
17. Kanda M, Fujii T, Takami H, et al. Combination of the serum carbohydrate antigen 19-9 and carcinoembryonic antigen is a simple and accurate predictor of mortality in pancreatic cancer patients. Surgery today. 2014;44(9):1692-1701.
18. Distler M, Pilarsky E, Kersting S, Grutzmann R. Preoperative CEA and CA 19-9 are prognostic markers for survival after curative resection for ductal adenocarcinoma of the pancreas - a retrospective tumor marker prognostic study. International journal of surgery (London, England). 2013;11(10):1067-1072.
19. Wu L, Huang P, Wang F, et al. Relationship between serum CA19-9 and CEA levels and prognosis of pancreatic cancer. Annals of translational medicine. 2015;3(21):328.
20. Tsavaris N, Kosmas C, Papadoniou N, et al. CEA and CA-19.9 serum tumor markers as prognostic factors in patients with locally advanced (unresectable) or metastatic pancreatic adenocarcinoma: a retrospective analysis. Journal of chemotherapy (Florence, Italy). 2009;21(6):673-680.
21. Reitz D, Gerger A, Seidel J, et al. Combination of tumour markers CEA and CA19-9 improves the prognostic prediction in patients with pancreatic cancer. Journal of clinical pathology. 2015;68(6):427-433.
22. Lee KJ, Yi SW, Chung MJ, et al. Serum CA 19-9 and CEA levels as a prognostic factor in pancreatic adenocarcinoma. Yonsei medical journal. 2013;54(3):643-649.
23. Kim YC, Kim HJ, Park JH, et al. Can preoperative CA19-9 and CEA levels predict the resectability of patients with pancreatic adenocarcinoma? Journal of gastroenterology and hepatology. 2009;24(12):1869-1875.
24. van der Geest LGM, Lemmens V, de Hingh I, et al. Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. The British journal of surgery. 2017;104(11):1568-1577.
25. Brockhaus M, Magnani JL, Blaszczyk M, et al. Monoclonal antibodies directed against the human Leb blood group antigen. The Journal of biological chemistry. 1981;256(24):13223-13225.
26. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer research. 1987;47(20):5501-5503.
27. Victorzon M, Haglund C, Lundin J, Roberts PJ. A prognostic value of CA 19-9 but not of CEA in patients with gastric cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 1995;21(4):379-384.
28. Filella X, Molina R, Grau JJ, et al. Prognostic value of CA 19.9 levels in colorectal cancer. Annals of surgery. 1992;216(1):55-59.
29. Pezzuto A, Spoto C, Vincenzi B, Tonini G. Short-term effectiveness of smoking-cessation treatment on respiratory function and CEA level. Journal of comparative effectiveness research. 2013;2(3):335-343.
30. Petrushnko W, Gundara JS, De Reuver PR, O'Grady G, Samra JS, Mittal A. Systematic review of peri-operative prognostic biomarkers in pancreatic ductal adenocarcinoma. HPB : the official journal of the International Hepato Pancreato Biliary

Association. 2016;18(8):652-663.
31. Swords DS, Firpo MA, Scaife CL, Mulvihill SJ. Biomarkers in pancreatic adenocarcinoma: current perspectives. OncoTargets and therapy. 2016;9:7459-7467.
32. Ruckert F, Pilarsky C, Grutzmann R. Serum tumor markers in pancreatic cancer-recent discoveries. Cancers. 2010;2(2):1107-1124.
33. Dong D, Jia L, Zhang L, et al. Periostin and CA242 as potential diagnostic serum biomarkers complementing CA19.9 in detecting pancreatic cancer. Cancer science. 2018;109(9):2841-2851.
34. Luo G, Xiao Z, Long J, et al. CA125 is superior to CA19-9 in predicting the resectability of pancreatic cancer. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2013;17(12):2092-2098.
35. Liu R, Chen X, Du Y, et al. Serum microRNA expression profile as a biomarker in the diagnosis and prognosis of pancreatic cancer. Clinical chemistry. 2012;58(3):610-618.
36. Melo SA, Luecke LB, Kahlert C, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature. 2015;523(7559):177-182.
37. Holzapfel K, Reiser-Erkan C, Fingerle AA, et al. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. Abdominal imaging. 2011;36(2):179-184.
38. Kim HW, Lee JC, Paik KH, et al. Adjunctive role of preoperative liver magnetic resonance imaging for potentially resectable pancreatic cancer. Surgery. 2017;161(6):1579-1587.
39. Jeon SK, Lee JM, Joo I, et al. Magnetic resonance with diffusion-weighted imaging improves assessment of focal liver lesions in patients with potentially resectable pancreatic cancer on CT. European radiology. 2018.
40. Bipat S, Phoa SS, van Delden OM, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. Journal of computer assisted tomography. 2005;29(4):438-445.
41. Chang L, Stefanidis D, Richardson WS, Earle DB, Fanelli RD. The role of staging laparoscopy for intraabdominal cancers: an evidence-based review. Surgical endoscopy. 2009;23(2):231-241.
42. Morris S, Gurusamy KS, Sheringham J, Davidson BR. Cost-effectiveness of diagnostic laparoscopy for assessing resectability in pancreatic and periampullary cancer. BMC gastroenterology. 2015;15:44.
43. Gutowski M, Framery B, Boonstra MC, et al. SGM-101: An innovative near-infrared dye-antibody conjugate that targets CEA for fluorescence-guided surgery. Surgical oncology. 2017;26(2):153-162.
44. Hoogstins CES, Boogerd LSF, Sibinga Mulder BG, et al. Image-Guided Surgery in Patients with Pancreatic Cancer: First Results of a Clinical Trial Using SGM-101, a Novel Carcinoembryonic Antigen-Targeting, Near-Infrared Fluorescent Agent. Annals of surgical oncology. 2018.