ORIGINAL RESEARCH

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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☆

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ABSTRACT

Background: The prognosis for patients with ductal adenocarcinoma of the pancreas (PDAC) remains poor even after curative resection. Carbohydrate antigen 19-9 (CA 19-9) and the carcinoembryonic antigen (CEA) are the most widely used serum-based tumor markers for the diagnosis and follow up of pancreatic cancer. In our analysis we aim to assess the prognostic value of a combination of both tumor markers in patients with pancreatic ductal adenocarcinoma (PDAC).

Patients and methods: Between 01/1995 and 08/2012 we performed a total of 264 pancreatic resections due to PDAC. Patients were stratified into 3 groups in regard to their preoperative tumor marker levels. Survival was compared between the groups using Kaplan Meier analysis and log rank test. Univariate subgroup analysis and multivariate analysis were performed.

Results: For 259 cases complete follow up could be obtained. In patients with low preoperative CEA and CA 19-9 levels (group 1 $n = 91$) the mean survival was 33.3 month (CI 95% 25.1—41.5). If one of the analyzed tumor markers (CEA/CA19-9) was preoperatively elevated above the cut-off level (group 2 $n = 106$) mean survival was 28.5 month (CI 95% 22.1—35.1). 62 patients showed preoperative elevation of both, CEA and CA 19-9 (group 3); mean survival in this group was 23.9 month (CI 95% 13.9—33.9), $p > 0.01$. Multivariate analysis confirmed preoperative CEA/CA 19-9 level as independent prognostic factor (HR 1.299).

Conclusion: Preoperative CEA and CA 19-9 levels correlate with patient prognosis after curative pancreatic resection due to PDAC. This is especially true for the most frequently pT 3/4 stages of PDAC. Even if CEA and CA 19-9 might not be appropriate for screening, its serum levels should therefore be determined prior to operation and taken into account when resectability or operability is doubtful.

1. Introduction

The prognosis for patients with ductal adenocarcinoma of the pancreas (PDAC) remains poor. Today, tumor resection is the only therapeutic option to achieve long-term survival.

However, only a small number of patients (30—40%) present with a resectable tumor at the time of diagnosis.[1,2] The overall 5-year survival after pancreatic head resection for cancer has been reported to range between 10 and 25%.[3—5] An adjuvant chemotherapy, which improves patient survival, should be routinely used.[6,7] However, there are patients that relapse shortly after the tumor resection and, therefore, have only a limited life span even after R0 resection. Clinical parameters that have been reported to be the significant prognostic factors for patient survival after tumor resection are as follows: age, tumor size, nodal and margin status and tumor grade.[4,8—10]

Imaging methods are not accurate enough to detect early lesions and also the differentiation of malignant from benign pancreatic lesions is an ordinary problem. For this the evaluation of molecular markers for early detection of pancreatic cancer is essential. An "ideal" tumor marker possesses high sensitivity enabling to identify the disease in a screening population without symptoms. Furthermore the marker should be useful for staging, prognosis, evaluation of response to therapy and follow up of PDAC.

A wide variety of tumor- and biomarkers in the serum, pancreatic tissue, pancreatic juice and stool have been studied

during the last decades.[11] Nevertheless utility of those markers is often limited by poor sensitivity, high false positive rates and lack of large scale validation.[12] Currently, the assessment of the serum tumor markers CA 19-9 and CEA offer the best clinical use in PDAC.

1.1. CA 19-9

The carbohydrate antigen 19-9 (CA 19-9) is the most widely assessed serum-based tumor marker for the diagnosis and follow up of PDAC.[13] CA 19-9 is a tumor associated antigen, initially isolated as a colorectal cancer antigen, but also presented in epithelial cells of the gallbladder, biliary system, pancreas and stomach.[11,14] CA 19-9 is related to the Lewis blood group antigens and only the 90–95% of patients belonging to the Le ($\alpha-\beta+$) or Le ($\alpha+\beta-$) blood groups will express the CA 19-9 antigen.[15,16] The diagnostic value of CA 19-9 for the detection of PDAC has been demonstrated in several studies.[13,15,17–20] Sensitivity of CA 19-9 ranges between 69% and 93%. Accordingly, about 30% of the patients with PDAC do not show elevated levels of CA 19-9.[13,19,20] Specificity for PDAC reaches up to 90% with a cut off level at 37 U/ml.[21] Notably, in regard to the differential diagnoses in PDACs, CA 19-9 can also be elevated in patients with liver cirrhosis and benign inflammatory or cholestatic diseases of the pancreaobiliary tract.[21,22] Unfortunately, due to lower levels in localized PDACs, CA 19-9 is not useful for the early detection of small tumors.[19,21]

In clinical practice, CA 19-9 is most commonly used for assessment of prognosis and monitoring of response or recurrence of a PDAC.[13,23]

1.2. CEA

The carcinoembryonic antigen (CEA) was the first tumor marker used for diagnostics of PDACs starting in the seventies. After decades, CEA nowadays has been replaced by markers with a higher diagnostic performance such as CA 19-9. However, several recent studies report low levels of CEA in normal tissue and elevated levels in presence of pancreatic cancer.[24,25] Specificity of CEA is up to 100% with a range between 25 and 56%.[24,26–28] Today CEA is mostly used for the analysis of the fluid of cystic pancreatic lesions (e.g. IPMN of the pancreas). Elevated levels of CEA in the cyst fluid are predictive for malignancy in IPMN of the pancreas.[29]

In this study we aimed to investigate the prognostic value of the preoperative tumor markers CEA and CA 19-9 alone or in combination in patients with PDAC.

2. Patients and methods

2.1. Patients

Between 01/1995 and 08/2012 we performed a total of 1251 pancreatic operations at our institution. Two hundred sixty-four pancreatic resections were performed for PDAC with curative intent. In 259 cases complete follow up could be obtained. Eight hepatobiliary surgeons performed $n = 202$ pancreatic head resections (PPPD/Whipple), $n = 38$ distal pancreatectomies, $n = 11$ total pancreatectomies and $n = 8$ other pancreatic resections (segmental or central pancreatic resections). Tumor localizations were: $n = 209$ head tumors, $n = 38$ tumors in the tail of the pancreas and $n = 12$ tumors in the body of the pancreas. In all cases, the diagnosis of PDAC was confirmed by postoperative histopathological examination of the specimen. For this retrospective analysis we excluded patients who underwent palliative pancreatic resections for PDAC or patients with distal cholangiocarcinoma, duodenal carcinoma, neuroendocrine tumors, cyst-adenocarcinoma, solid and papillary tumors, and metastatic disease. Included patients were stratified into 3 groups in regard to their preoperative CEA and CA

19-9 levels (<u>Group 1</u>: CEA/CA 19-9 within normal ranges, <u>Group 2</u>: CEA *or* CA 19-9 above the cut off level and <u>Group 3</u>: CEA and CA 19-9 both above cut off level) [Table 1].

2.2. Tumor marker measurements

Peripheral venous blood samples were taken from every patient at time of presentation before any therapeutic procedure. These samples were centrifuged and stored at $-20\ ^\circ C$ until they were analyzed. CEA and CA 19-9 analysis was performed with Liaison® Analyzer by Dia-Sorin (2-step sandwich chemiluminescence immunoassay, using directly coated magnetic particles (solid phase) and an isoluminol derivative (conjugate), (Dia-Sorin Diagnostic Group, Dietzenbach, Germany, http://www.diasorin.com).

2.3. Data collection

The medical records from a prospective database of patients who underwent a pancreatic resection for PDAC were analyzed retrospectively for each case. In accordance with the guidelines for human subject research, approval was obtained from the Ethics committee at the Carl Gustav Carus University Hospital. All operated patients signed informed consent before surgery. The survey data were complemented with the clinical notes of the patients' physicians and surgeons. The information regarding the deceased patients was obtained from family members or from their general practitioner. Patients were followed up until death; median postoperative follow-up time was 38 month.

2.4. Statistical analysis

The preoperative tumor marker levels of CEA and CA 19-9 were correlated with the patients clinical characteristics from our prospective pancreatic database. The statistical analyses were

Table 1
Demographics and pathohistological data of patient cohort ($n = 259$) and stratification in regard to the preoperative CEA and CA 19-9 levels (Group 1–3).

	Group 1 ($n = 91$) CEA/CA 19-9 below cut-off level	Group 2 ($n = 106$) CEA *or* CA 19-9 above cut-off level	Group 3 ($n = 62$) CEA/CA 19-9 above cut-off level	*p*-Value
Sex $n =$ (m/f)	49/42	62/44	33/29	0.534[a]
Age y ($\pm$SD)	62.5 ($\pm$12.2)	63.2 ($\pm$12.4)	67.4 ($\pm$12.1)	0.657[a]
Mean-survival (month)	33.3 (CI 95% 25.1–41.5)	28.5 (CI 95% 22.1–35.1)	23.9 (CI 95% 13.9–33.9)	0.013[a]
Tumor localization				
Head	79	81	49	0.743[a]
Body	4	6	2	
Tail	8	19	11	
Type of surgery				
Head resections	77	79	46	0.411[a]
Total Pancreatect	4	5	2	
Left resections	9	17	12	
Others	1	5	2	
pT 1/2	5	19	2	0.004[a]
pT 3/4	63	79	57	
pN 0	23	35	21	0.987[a]
pN +	43	61	38	
pM 0	64	91	55	0.952[a]
pM +	5	8	4	
G 1/2	42	46	33	0.121[a]
G 3/4	24	51	26	
R 0	65	73	46	0.876[a]
R 1	22	26	13	
R 2	4	5	1	
R x	–	2	2	

[a] Chi–Quadrat Test.

performed using SPSS for Windows, version 21.0 (SPSS, Inc., Chicago, IL). All clinical and pathological characteristics were stratified to build categorical or nominal variables. Categorical data were analyzed using Chi Square test. The estimates of patient survival were generated using the Kaplan−Meier method. Continuous data are presented as 95% confidence intervals (95% CI) and/or standard deviation (SD). Survival is described as mean or median survival with CI 95%. The comparisons of survival were made using the log-rank test. Next, we performed a subgroup analysis for the different tumor T-stages in correlation to CEA/CA 19-9 level. For multivariate analysis we used a Cox regression analysis with stepwise backwards elimination based on the likelihood ratios to test for independent predictors of survival.

Cut-off levels for CEA and CA 19-9 were determined at 3 ng/ml and 75 U/ml, respectively (as recommended by the manufacturer of the test kits). A p-value <0.05 was considered significant.

3. Results

3.1. Patient cohort

From 01/1995 to 08/2012, 264 patients underwent pancreatic resections due to ductal adenocarcinoma of the pancreas. As mentioned above the 259 patients with complete follow up were distributed to groups 1-3 according to their preoperative CEA and CA 19-9 levels. A total of five patients were excluded from the analysis due to incomplete information on the preoperative tumor markers, missing follow up after resection or incomplete tumor staging. In 91 cases preoperative CEA and CA 19-9 values were both under the used cut-off levels (group 1), in 106 patients either CEA or CA 19-9 were above the cut-off level and a total of 62 patients showed preoperative elevation of CEA and CA 19-9 [Table 1]. The three groups of patients were comparable in regard to age and sex. However, in concern to the tumor t-staging statistical analysis showed significant differences between the 3 groups ($p = 0.004$) [Table 1]. Therefore we performed a subgroup analysis for the pT 1/2 and pT3/4 patients [Table 2].

3.2. Preoperative tumor marker level and survival

For each group we performed a Kaplan Meier analysis and comparisons between the groups were made by the log rank test [Fig. 1]. In patients with low preoperative CEA and CA 19-9 levels (Group 1 $n = 91$) the mean survival was 33.3 month (CI 95% 25.1−41.5) after curative resection of a PDAC. If one of the analyzed tumor markers (CEA/CA19-9) was elevated above the cut-off level preoperatively, patients were classified into group 2 ($n = 106$). The estimated overall survival for patients of Group 2 was 28.5 month (CI 95% 22.1−35.1). In 62 patients CEA and CA 19-9 were both elevated (Group 3) above the cut off level of ≤3 ng/ml and ≤75 U/ml, respectively. Preoperative elevation of both tumor markers was associated with a poorer survival (23.9 month (CI 95% 13.9−33.9) for Group 3) [Fig. 1]. Log rank test showed significant differences ($p < 0.01$) between these 3 groups.

3.3. Univariate analysis

Due to statistical differences concerning t-staging ($p = 0.004$) between the 3 groups a univariate subgroup analysis of the patients

with pT 1/2 and pT3/4 tumors was performed. Univariate analysis of subgroup pT 1/2 ($n = 26$) showed a median survival of 25.9 months for group 1 and 17.1 months for group 2 patients as 8.3 months for group 3, respectively [Fig. 2]. In the pT 1/2 subgroup no statistical significance between the different CEA/CA19-9 groups (1−3) was detected ($p = 0.109$) [Table 2]. Subgroup analysis for pT 3/4 tumors ($n = 199$) showed that preoperative tumor marker level of CEA and CA 19-9 is an independent predictor of patient survival ($p = 0.007$) [Table 2]. Median survival of the pT 3/4 subgroup was; 27.7 months for group 1, 19.7 months for group 2 and 13.8 months for group 3 [Fig. 3].

3.4. Multivariate analysis

Available clinical data which may influence patients median survival (q.v. Table 1) was tested using a multivariate analysis. There, preoperative elevation of CEA/CA 19-9 above the cut off levels ($p < 0.001$), pT 1/2 stage ($p = 0.040$) and positive nodal status (pN+) ($p = 0.031$) could be identified as independent factors influencing patients survival after pancreatic resection (HR 1.299, 0.595 and 1.470, respectively).

4. Discussion

The aim of this study was to clarify the role of preoperative CEA/CA 19-9 measurement as a prognostic marker after curatively intended resection of a PDAC. Levels of CEA and CA 19-9 have been widely described to be elevated in up to 85% of the patients with PDAC.[13,20,24,27,30] CEA and CA 19-9 can predict survival after pancreatic resection and are markers for recurrent disease after curative resection of a PDAC.[24,31] Specificity of CEA and CA 19-9 for PDAC ranges between 90 and 100%.[21,26,27]

The main problem of both markers, and especially for CEA, is a low and wide-ranging sensitivity (30−90%) for detection of a PDAC.[13,19,20,24] About 60% of the patients with PDAC do not have elevated levels of CEA and 30% do not show elevation of CA 19-9.[13,19,20] These findings could be confirmed by our analysis. In our cohort about 35% (Group 1 $n = 91$) of the patients with PDAC (Group 1, $n = 91$) presented without any preoperative elevation of CEA or CA 19-9.

Furthermore, CA 19-9 and CEA undergo biliary excretion, and serum levels may be artificially increased due to liver cirrhosis and benign inflammatory or cholestatic diseases of the pancreaobiliary tract.[21,22,32,33] However, elevated serum levels of CA 19-9 and CEA correlate with tumor differentiation and extent of a PDAC.[13,19,20,34] Unfortunately, due to the low levels in localized PDACs, CA 19-9 and CEA are not useful for early detection of small tumors.[19,21] Due to this findings we, as other authors, do not advocate CEA or CA 19-9 as a screening tool for PDAC in asymptomatic patients.[24]

The merit of CEA and CA 19-9 to provide meaningful prognostic information and allow for patient stratification into survival groups has been investigated before.[20,34−39] Unique in our analysis is the stratification of the patients into 3 groups according to their preoperative levels of CEA and CA 19-9. We found that preoperative tumor marker values below the cut off level (CEA ≤3 ng/ml and CA 19-9 ≤75 U/ml) correlate with an improved survival after curative resection of a PDAC. The mean survival for these patients (group 1)

Table 2
Univariate analysis of median survival for T-stage subgroups and subgroups of CEA/CA 19-9 (Groups 1−3).

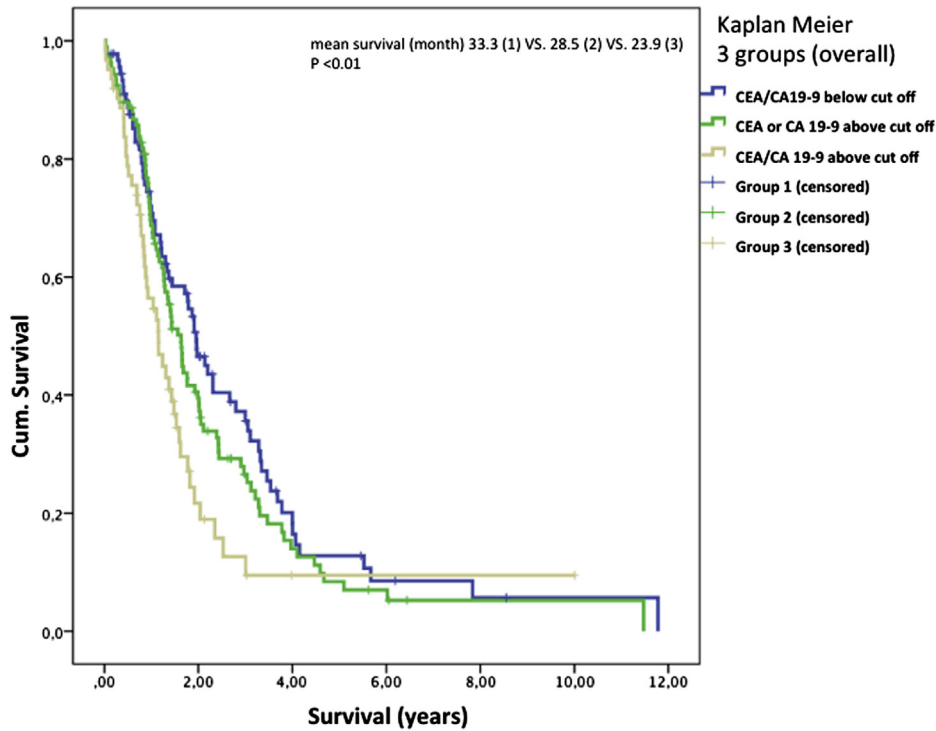| Subgroups	Group 1 CEA/CA 19-9 below cut-off level	Group 2 CEA or CA 19-9 above cut-off level	Group 3 CEA/CA 19-9 above cut-off level	p-Value (log rank)
pT 1/2 ($n = 26$) Median-Survival (month)	25,9 (CI 95% 10.9−41,7)	17,1 (CI 95% 4.9−29.2)	8.3 (CI 95% n.a.)	0.190
pT 3/4 ($n = 199$) Median-Survival (month)	27.7 (CI 95% 15.2−40.1)	19.7 (CI 95% 15.4−24.1)	13.8 (CI 95% 10.8−16.8)	0.007

Fig. 1. Kaplan Meier analysis of patients with PDAC in regard to their preoperative levels of CEA and CA 19-9 (Group1-3).

was 33.3 month (CI 95% 25.1–41.5), while preoperative tumor marker values above the cut off levels led to a more unfavorable prognosis. Patients showing preoperative elevation of CEA *and* CA 19-9 (Group 3) had a significantly worse mean survival ($p < 0.01$) than patients presenting with only one elevated tumor marker above the cut off level (group 2) (28.5 month CI 95% 22.1-35.1 vs. 23.9 month CI 95% 13.9–33.9) [Table 1 and Fig. 1]. This is especially

true for patients with pT 3/4 tumors as demonstrated in the univariate subgroup analysis [Table 2, Fig. 3]. Furthermore, multivariate analysis identified preoperative elevated CEA/CA 19-9 levels as an independent risk factor influencing patient survival (HR 1.299) [Table 3].

These findings correlate well to results in literature. Berger et al. stratified 129 surgically resected pancreatic cancer patients into 4
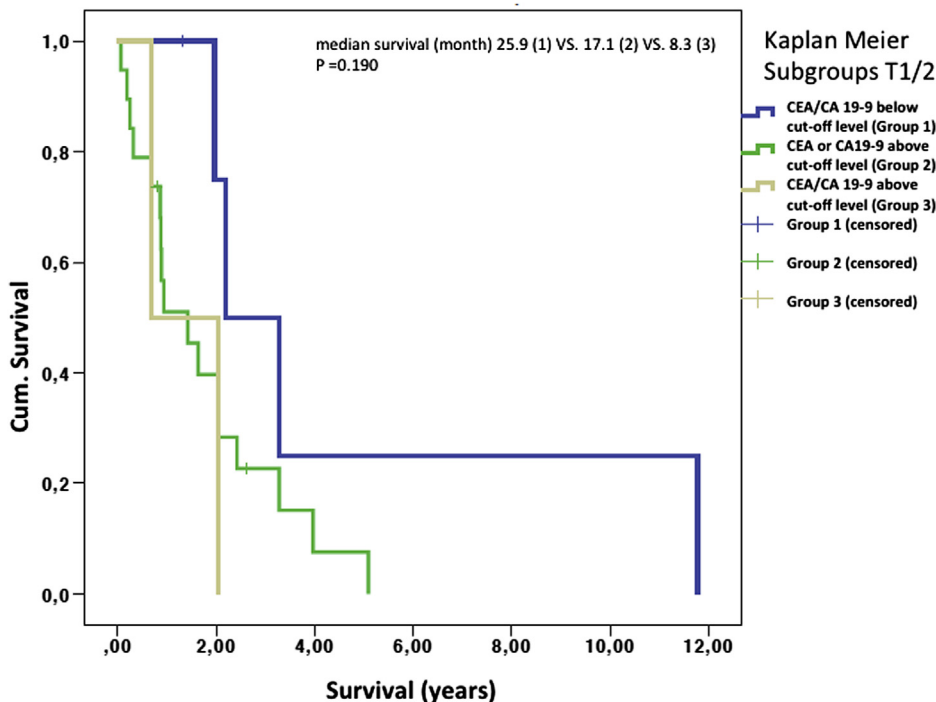

Fig. 2. Kaplan Meier analysis of patients with PDAC for subgroup T 1/2 and subgroups of CEA/CA 19-9 (1–3).
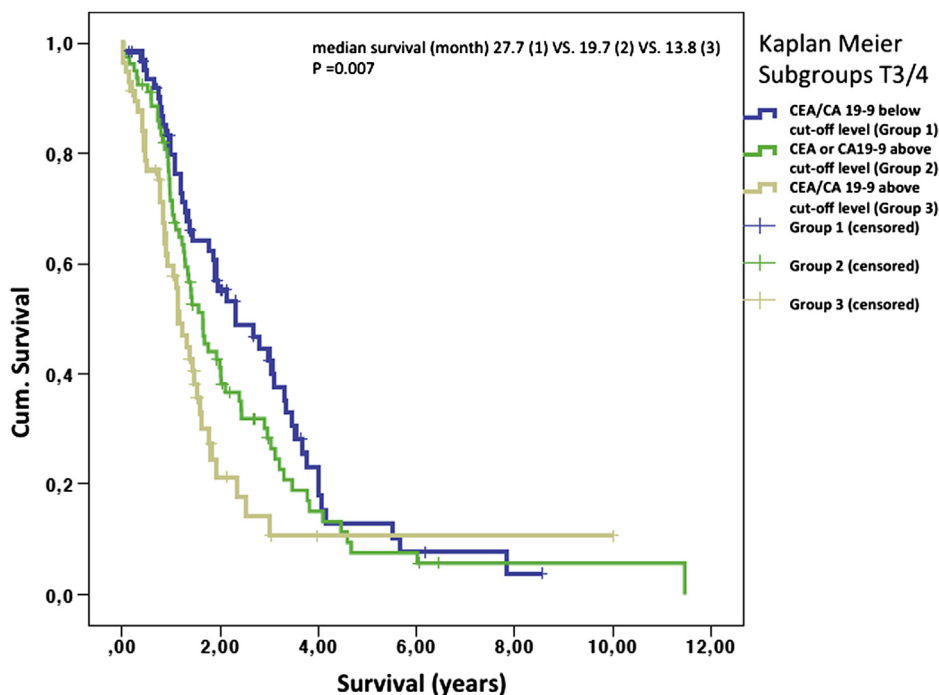
Fig. 3. Kaplan Meier analysis of patients with PDAC for subgroup T 3/4 and subgroups of CEA/CA 19-9 (1–3).

groups based on their pre-operative CA 19-9 level (undetectable, normal (<37 U/mL), 38–200 U/mL, and >200 U/mL). Patients with undetectable pre-operative CA 19-9 serum levels and those with levels of <37 U/mL had an improved median survival (32 and 35 months, respectively) compared to patients with CA 19-9 serum levels between 38 and 200 U/mL or >200 U/mL (22 and 16 months, respectively).[35] Smith et al. evaluated preoperative CA 19-9 serum levels in 109 pancreatic cancer patients who underwent a pancreatoduodenectomy and noted a median survival of only 10.4 months in patients with a preoperative CA19-9 level >150 U/mL (*n* = 64), compared to a median survival of 22.1 months in patients with a CA19-9 serum level ≤150 U/mL (*n* = 45, *p* = 0.012).[36]

These studies and our results support the conclusion that normal or low preoperative levels of CEA and/or CA 19-9 independently predict longer survival after curative pancreatic resection due to PDAC, whereas preoperatively elevated serum levels of both, CEA/CA 19-9, are associated with a poor prognosis. However, it has to be kept in mind that due to the different cut off levels used in the literature the comparability of the studies is limited. Furthermore, due to the retrospective character of this analysis, we could not determine the ratio of patients receiving adjuvant chemotherapy. From prior analysis of our database we know that about 50% of our patients have received adjuvant chemotherapy and that there is a heterogeneity of the chemotherapeutic regimes (i.e., mainly gemcitabine).[39]

Furthermore, in our study the multivariate analysis showed that T-status (pT 1/2: HR 0.595) and lymphnode involvement (pN+: HR 1.470) were also factors influencing patient survival after resection for PDAC. These results have already been described by other authors like Riediger et al. before.[10] Here it is worth mentioning that especially the lymphnode ratio is crucial as a prognostic factor and not only the N-status.

5. Conclusion

In conclusion, we could show that preoperatively elevated CEA and CA 19-9 can be used as additional information to estimate patients' prognosis. This is especially true for the most frequent pT 3/4 stages of PDAC. Moreover, T stage and N-status could be identified as predictive factors of survival after resection. Although CEA and CA 19-9 might not be appropriate for screening, its serum levels should therefore be determined in patients prior to operation. High preoperative serum levels of CEA and CA 19-9 should be taken into account by the surgeon when resectability or operability is doubtful.

Table 3
Multivariate analysis of factors that influence median survival in patients after pancreatic resection for PDAC.

	HR	95% confidence interval HR		*P* value
		Lower	Upper	
Step 1				
CEA/CA19-9 (elevated)	1.296	1.124	1.495	<0.001
pT 1/2	0.590	0.359	0.972	0.038
G 3/4	1.282	0.932	1.765	0.127
pN+	1.461	1.020	2.091	0.038
pM+	1.070	0.604	1.894	0.817
Step 2				
CEA/CA19-9 (elevated)	1.296	1.124	1.494	<0.001
pT 1/2	0.592	0.360	0.974	0.039
G 3/4	1.278	0.930	1.755	0.130
pN+	1.472	1.035	2.094	0.032
Step 3				
CEA/CA19-9 (elevated)	1.299	1.127	1.496	<0.001
pT 1/2	0.595	0.362	0.977	0.040
pN+	1.470	1.036	2.085	0.031

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