

Prognostic Impact of Presurgical CA19-9 Level in Pancreatic Adenocarcinoma: A Pooled Analysis

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Abstract

BACKGROUND: Presurgical carbohydrate antigen 19-9 (CA19-9) level predicts overall survival (OS) in resected pancreatic adenocarcinoma (PaC). The aim of this pooled analysis was to evaluate if presurgical CA19-9 level can also predict local control (LC) and distant metastasis-free survival (DMFS). **METHODS:** Seven hundred patients with PaC from eight institutions who underwent surgical resection ± adjuvant treatment between 2000 and 2014 were analyzed. Patients were divided based on four presurgical CA19-9 level cutoffs (5, 37, 100, 353 U/ml). Weibull

regression model to identify independent predictors of OS on 404 patients with complete information was fitted. **RESULTS:** Median follow-up was 17 months (range: 2-225 months). Univariate analysis showed a better prognosis in pT1-2, pN0, diameter <30 mm, or grade 1 tumors and in patients undergoing R0 resection, distal pancreatectomy, or adjuvant chemotherapy and with lower CA19-9 levels. Five-year OS, LC, and DMFS were as follows: CA19-9 <5.0: 5.7%, 47.2%, 17.0%; CA19-9 5.1-37.0: 37.9%, 63.3%, 46.0%; CA19-9 37.1-100.0: 27.1%, 59.4%, 39.0%; CA19-9 100.1-353.0: 17.4%, 43.4%, 26.7%; CA19-9 >353.1: 10.9%, 50.2%, and 23.4%, respectively. At multivariate analysis, CA19-9 >100 and <353 level ($P=.002$), CA19-9 ≥ 353.1 ($P<.001$) level, G3 tumor ($P=.002$), and tumor diameter >30 mm ($P<.001$) correlated with worse OS. Patients treated with postoperative chemoradiation doses >50.0 Gy showed improved OS ($P<.001$). **CONCLUSION:** Presurgical CA19-9 predicts both OS and pattern of failure. Therefore, CA19-9 should be included in predictive models in order to customize treatments based on prognostic factors. Moreover, future studies should stratify patients according to presurgical CA19-9 level.

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Introduction

According to Cancer Stat Facts (National Cancer Institute, Surveillance, Epidemiology, and End Results program), 55,440 new cases of pancreatic carcinoma (PaC) are estimated in 2018, and 5-year survival was only 8.5% between 2008 and 2014 in the United States [1]. In Europe, PaC mortality has recently increased [2], and in the United States, PaC represents the fourth cause of cancer mortality, while in 2030, it will become the second leading cause of cancer mortality [3]. Prognosis is unfavorable even in the minority (20%) of patients with resectable disease despite the contribution of adjuvant therapies which have produced some marginal improvement in survival [4].

Based on these disappointing results, more effective and tailored adjuvant treatments are needed to improve patients' outcome. Furthermore, identification of cancer biology surrogate biomarkers able to define patient groups with higher risk of local recurrence and distant metastasis would be useful [5,6].

In 1979, Koprowski and colleagues first discovered carbohydrate antigen 19-9 (CA19-9) originally isolated from a human colorectal cancer cell line [7]. The prognostic role of presurgical CA19-9 has been suggested in patients with resected PaC [8,9]. Moreover, CA19-9 determination is rapid and cost-effective. Therefore, presurgical assessment of CA19-9 may improve patients' selection and stratification in clinical trials evaluating innovative PaC treatments different from the traditional approach of upfront surgery followed by adjuvant chemotherapy (CT) with or without postoperative chemoradiation (CRT).

However, evidence on the predictive role of CA19-9 is limited. In particular, studies evaluating the possibility to predict both local and distant failures are lacking. Based on this background, we analyzed a multicenter patient population treated with radical surgery for PaC. The aim of the analysis was to evaluate whether CA19-9 could predict local control (LC) and distant metastasis-free survival (DMFS) and to confirm in a large series its correlation with survival.

Material and Methods

A multicenter retrospective review of 1300 patients who underwent surgical resection of PaC with or without adjuvant treatment [CT, CRT, postoperative and/or intraoperative radiotherapy (RT)] from eight institutions [Roma, Madrid, Verona, Milano, Campobasso, Baltimore (two institutions), Rochester] was performed. A total of

700 patients with available presurgical CA19-9 value were identified and included in the analysis.

Data collection and design of this pooled analysis were presented in a previous publication [10]. Briefly, participating centers selected data of patients with PaC who underwent radical surgery \pm adjuvant therapies. Patients with metastatic disease, histology other than adenocarcinoma, ampullary and periampullary tumors, neoadjuvant treatment, intraoperative RT, and lack of presurgical CA19-9 value were not included in the analysis. Also, postoperative CRT treatment modalities were previously described [11]. Briefly, RT was administered with linear accelerators using multiple-field technique. Median prescribed total dose was 50.4 Gy in 1.8 Gy daily fractionation. Concomitant CT was based on 5-fluorouracil or gemcitabine, while adjuvant CT was based on gemcitabine in most patients. Patients were treated between 2000 and 2014. After the treatment, most patients underwent physical examination, complete blood count, and computed tomography scan of chest and abdomen every 3 months in the first 2 years, every 6 months from the third to fifth year, and annually thereafter. In some patients treated before 2002, computed tomography scans were alternated with abdominal ultrasound and chest X-rays. Follow-up visits and imaging studies were anticipated in case of symptoms.

In this analysis, patients were divided according to presurgical CA19-9 levels based on four different cutoffs: ≤ 5 U/ml, 37 U/ml, 100 U/ml, and 353 U/ml and five relative CA19-9 classes: 0.0-5.0, 5.1-37.0, 37.1-100, 100.1-353.0, >353.1 U/ml. The first cutoff (≤ 5 U/ml) was applied to discriminate patients who are Lewis antigen negative and thus unable to express CA19-9 but similar to what was done in previous studies [6,12,13]. The second cutoff (37 U/ml) represented the upper limit of the normal reference CA19-9 value among normal subjects. The third cutoff (100 U/ml) was selected in analogy to several previous publications [14–16]. The fourth cutoff (353 U/ml) was the median value of patients with CA19-9 values >100 U/ml.

Continuous variables were expressed as median and range, while categorical variables were presented as number and percentages. Trend for trend across ordered variables was studied by means of score test for linear trend of the log odds. Survival functions were plotted using the Kaplan-Meier method and compared through the log-rank test or the modified log-rank test for trend (ordered variables) [17].

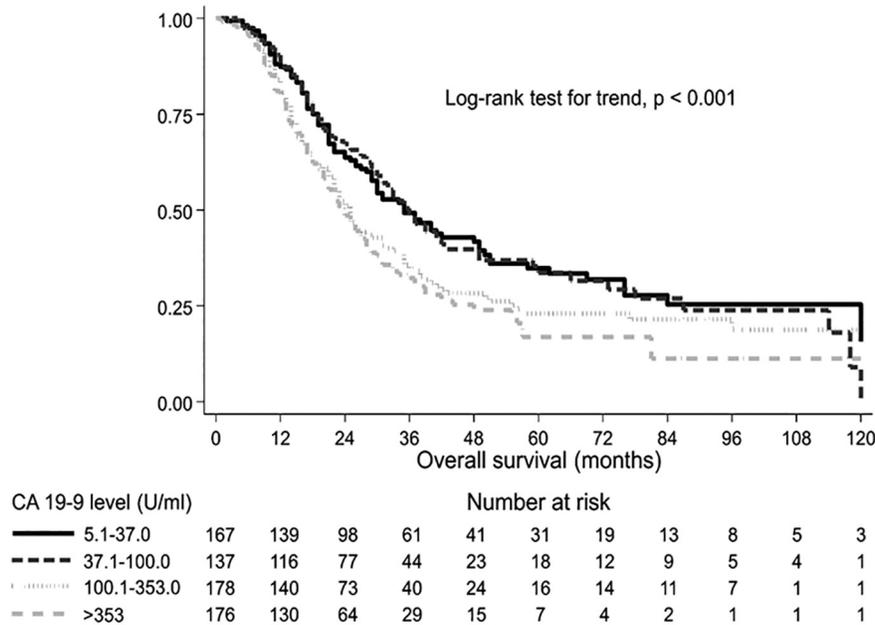


Figure 1. Overall survival by presurgical CA19-9 level. Kaplan-Meier survival curves and log-rank test adjusted by center.

The correlation between presurgical CA19-9 values and outcomes was studied both on the general population of 700 patients and on a subgroup of 404 patients with complete data also in terms of grading, margins status, and stage.

The analysis presented in Figures 1-3 and in the supplementary material was adjusted by participating center to account for baseline survival differences among hospitals. We adapted the Weibull regression models to study predictors of OS assuming shared frailty (gamma distributed) by participating center to account for latent center-level effects [18]. The Weibull distribution was chosen based

on preliminary analysis of the baseline hazard function. At first, we fitted spline Weibull survival regression models to explore the shape of the association between CA19-9 levels and OS using data of all patients [19]. Covariates included in multivariable models were selected with a stepwise backward elimination (P removal $\geq .10$; P addition $< .10$) based on likelihood ratio test. Median OS expressed in months was estimated as average marginal effects.

Statistical analysis was carried out using Stata 12.1 SE (Stata Corp, College Station, TX). All tests were two-sided, and a P value $< .05$ was considered statistically significant.

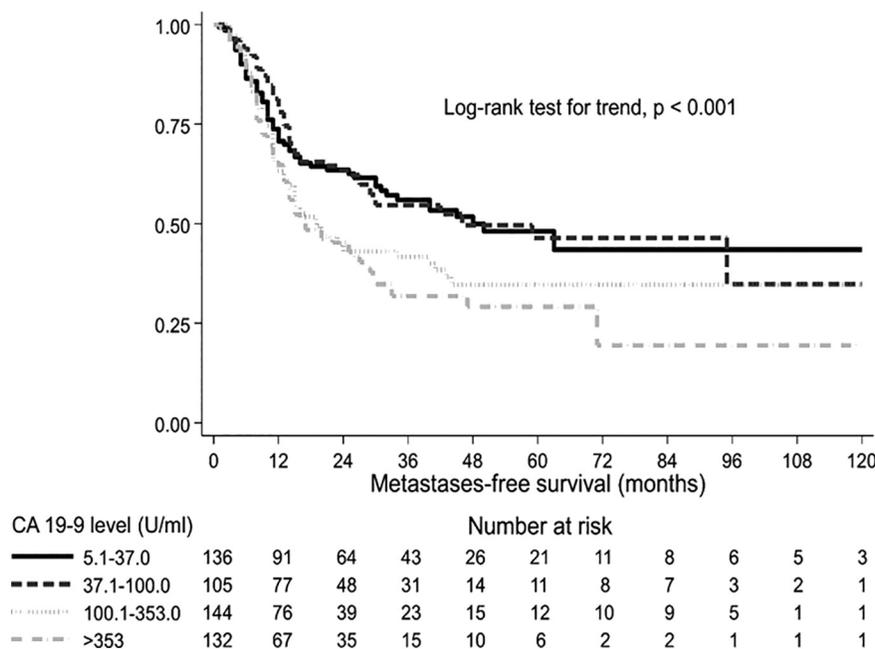


Figure 2. Distant metastases-free survival by presurgical CA19-9 level. Kaplan-Meier survival curves and log-rank test adjusted by center.

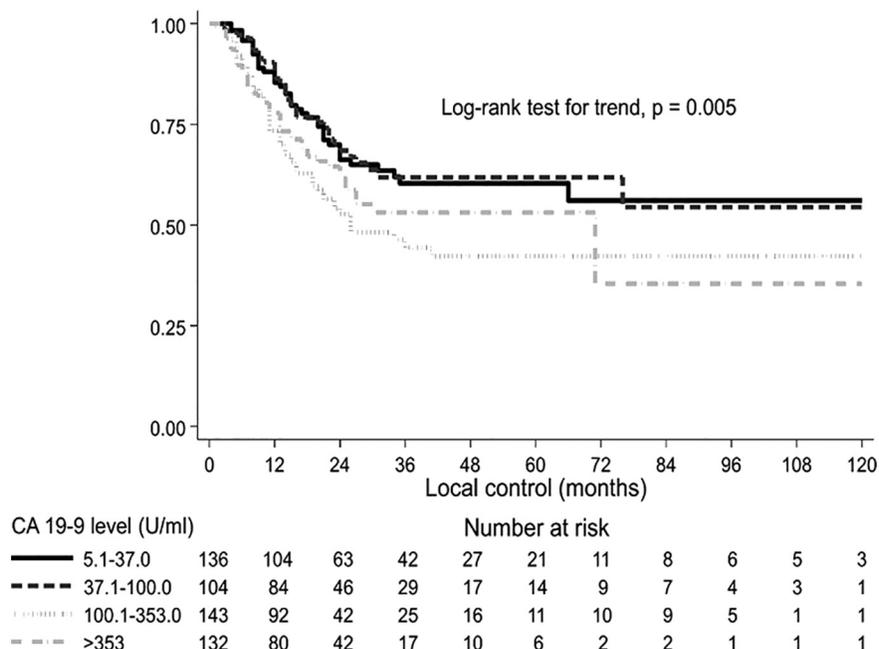


Figure 3. Local control by presurgical CA19-9 level. Kaplan-Meier survival curves and log-rank test adjusted by center.

Results

Based on the inclusion criteria, 700 patients with available presurgical CA19-9 value were included in this pooled analysis. The median age was 63 years (range: 17-86 years), and the median follow-up was 17 months (range: 2-225 months). Four hundred ninety-four patients (70.6%) underwent pancreaticoduodenectomy, 99 patients (14.1%) distal pancreatectomy, and 34 patients (4.9%) total pancreatectomy.

Table 1 shows patients characteristics and survival results in details. Univariate analysis showed a better prognosis in pT1-2, pN0, diameter <30 mm, or grade 1 tumors, and in patients undergoing R0 resection, distal pancreatectomy, or adjuvant chemotherapy and with lower CA19-9 levels.

Analyzing the association between presurgical CA19-9 level, excluding patients considered to be unable to express the marker (≤ 5 U/ml), those with a higher CA19-9 level had more advanced disease in terms of pathological tumor ($P < .001$) and nodal stage ($P < .001$), while no significant correlation with the margin status was recorded ($P = .256$) (Table 2).

Analyzing the impact of presurgical CA19-9 on outcome, increasing values of the marker were significantly correlated with worse OS ($P < .001$), LC ($P = .008$), and DMFS ($P < .001$), with the exception of patients with CA19-9 ≤ 5 U/ml (Table 3). Supplementary Material Figure shows the median OS curve fitted by presurgical CA19-9 levels. For patients with CA19-9 > 200 U/ml, median OS did not further worsen and was less than 2 years. Figures 1, 2, and 3 represent OS, DMFS, and LC stratified by presurgical CA19-9 classes and adjusted by participating center.

A further subgroup analysis of 404 patients with complete information was performed (Supplementary Material Table). Univariate analysis showed a better prognosis in females, in younger (< 59 years) patients, and in subjects undergoing postoperative CRT, R0 resection, or pancreaticoduodenectomy. Higher survival rates were recorded even in grade 1, pT1-2, and pN0 stage tumors and in PaCs with diameter < 30 mm. Furthermore, patients with a normal CA19-9 (5.1-37.0 U/ml) value showed better OS (median: 36 months) compared to the rest of the cohort.

At multivariable analysis, grade 3 (HR: 1.85, 95% CI 1.26-2.70, $P = .001$) and lymph node involvement (HR: 1.85, 95% CI: 1.35-2.53, $P < .001$) were associated with worse OS. Patients treated with a CRT dose > 50 Gy (HR: 0.38, 95% CI: 0.23-0.64, $P < .001$) showed a reduced risk of mortality. Median OS progressively worsened in patients with CA19-9 levels between 100.1 and 353.0 U/ml (HR: 1.79, 95% CI: 1.24-2.58, $P = .002$) and CA19-9 levels ≥ 353.1 (HR: 1.91, 95% CI: 1.33-2.74, $P < .001$).

Discussion

To the best of our knowledge, this study is one of the largest analyses on the prognostic role of presurgical CA19-9 value in resected PaC [10,20-22]. The results of this analysis clearly confirmed the role of CA19-9 as a predictor of OS. More interestingly, they demonstrated the role of this marker in predicting both LC and DMFS. Finally, they identified on an experimental basis a cutoff level (200 U/ml) able to define the patients' population with worse prognosis.

This analysis presents evident limits including the retrospective design, heterogeneity in the methods and timing of follow-up, and lack of correction of CA19-9 levels based on bilirubin values to prevent the confounding effect on the marker level due to the unavailability of this information. However, correcting CA19-9 values based on bilirubin levels does not seem to be mandatory as shown by the study of Hartwig and colleagues [7].

Our results confirm several previous reports [15,20,23-26] showing a relationship between higher presurgical CA19-9 level (> 100 U/ml or > 1000 U/ml) and poor prognosis. Only Kondo and colleagues reported lack of correlation between presurgical CA19-9 and OS, probably due to the relatively small number of patients included in their series [16].

Furthermore, in our analysis, a CA19-9 value > 200 U/ml was particularly indicative of poor OS and could be used as cutoff level for patients' stratification in future studies (Supplementary Material Figure).

Previous studies on carcinogenesis showed that CA19-9 is related to the Lewis blood group antigens by a mechanism of gene silencing of a sialyltransferase, which implies early abnormal synthesis and

Table 1. Patient Characteristics of the Analyzed Cohort with the Number of Patients and Percentage of the Total Number of Patients [%] and Survival Differences by Clinicopathologic and Treatment Details

Variable	Value	No. of Patients [%]	5-year OS [%]	Median OS [months]	P
Age	Median (range)	63 (17-86)			
Gender	Male	360 [51.4]	18.8	25	.099
	Female	340 [48.6]	25.8	26	
CA 19-9 level (U/ml)	0.0-5.0	39 [5.6]	5.7	25	<.001
	5.1-37.0	167 [23.9]	37.9	38	
	37.1-100.0	139 [19.9]	27.1	32	
	100.1-353.0	178 [25.4]	17.4	22	
	>353.1	177 [25.3]	10.9	20	
Tumor site	Head	583 [83.3]	20.8	25	.102
	Body	74 [10.6]	31.8	37	
	Tail	31 [4.4]	27.5	22	
	Unknown	12 [1.7]			
Type of pancreatectomy	PD	494 [70.6]	21.4	25	.032
	DP	99 [14.1]	31.7	35	
	TP	34 [4.9]	9.9	21	
	Unknown	73 [10.4]			
Grade	1	68 [9.7]	33.2	29	.001
	2	276 [39.4]	21.0	29	
	3	272 [38.9]	19.3	21	
	4	14 [2.0]	22.0	28	
	Unknown	70 [10.0]			
Margin status	R0	350 [50.0]	27.7	29	<.001
	R1	203 [29.0]	12.5	21	
	Unknown	147 [21.0]			
Tumor diameter (mm)	< 30	269 [38.4]	35.3	31	<.001
	≥ 30	223 [31.9]	17.4	22	
	Unknown	208 [29.7]			
pT stage	1	21 [3.0]	61.5	84	<.001
	2	78 [11.1]	27.5	36	
	3	549 [78.4]	19.5	24	
	4	44 [6.3]	23.6	22	
	Unknown	8 [1.2]			
pN stage	N0	208 [29.7]	36.5	34	<.001
	N+	486 [69.4]	16.1	23	
	Unknown	6 [0.9]			
Adjuvant CT	No	302 [43.1]	21.8	22	.009
	Yes	398 [56.9]	22.3	28	
Postoperative RT ± CCT	No	311 [44.4]	25.9	25	.271
	Yes	389 [55.6]	19.4	25	
RT dose (Gy)	<50.4	85 [12.2]	24.4	25	.660
	>50.4	222 [31.7]	20.1	26	
	Unknown	393 [56.1]			

CCT: concurrent CT; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; TP, total pancreatectomy.

accumulation of the sialyl Lewis-a [27,28]. Approximately 7%-10% of Caucasian individuals have Lewis α-β- phenotype [14,28] and therefore are unable to express this antigen.

In this analysis, contrary to the results reported by Berger and colleagues [9] and Hartwig and coworkers [6], nonsecretor patients showed a worse 5-year OS compared to those with CA 19-9 level between 5 and 37 U/ml (5.7% vs. 37.9%, respectively). Therefore, further analysis on the outcome of these patients' subgroups is justified to avoid undertreatment of this group of subjects.

Some previous studies reported a correlation between CA 19-9 and resectability [29,30]. These findings are confirmed by the relationship we observed between the five CA19-9 classes and tumor ($P<.001$) and nodal stage ($P<.001$). Our analysis also showed a significant impact of CA19-9 level on patients' outcome, independently of other well-known prognostic factors such as tumor grade and stage. These findings suggest a relationship between CA19-9 values with biological tumor aggressiveness and therefore the opportunity to include this marker in predictive models [30].

Table 2. Association between Presurgical CA19-9 Level and Tumor Stage, Nodal Stage, and Margins Status

Ca 19-9 Level (U/ml)	Tumor Stage		Nodal Stage		Margin Status	
	T1-2 (%)	T3-4 (%)	N0 (%)	N1 (%)	R0 (%)	R1 (%)
0.0-5.0	2.8	97.2	27.8	72.2	57.1	42.9
5.1-37.0	21.6	78.4	39.4	60.6	60.7	39.3
37.1-100.0	17.3	82.7	36.0	64.0	60.7	39.3
100.1-353.0	12.4	87.6	22.6	77.4	66.7	33.3
>353.1	9.6	90.4	24.3	75.7	65.9	34.7
P trend [*]	<.001		<.001		.256	

^{*} Score test for linear trend of the log odds across CA 19-9 level categories 5.1-37.0, 37.1-100.0, 100.1-353.0, and >353.1.

Table 3. Impact of Presurgical CA19-9 on LC and DMFS

Variable	Value (U/ml)	5-year LC (%)	Median LC (Months)	P	5-year DMFS (%)	Median DMFS (Months)	P
CA19-9	0.0-5.0	47.2	24	.008	17.0	20	<.001
	5.1-37.0	63.3	NR		46.0	45	
	37.1-100.0	59.4	NR		39.0	29	
	100.1-353.0	43.4	26		26.7	15	
	>353.1	50.2	71		23.4	14	

NR, not reached.

This study demonstrated a significant correlation between presurgical CA19-9 levels and LC and DMFS. Kim and colleagues [13] reported a worse DMFS in patients with higher CA19-9 values, while a correlation with LC was never reported before. It has been hypothesized that through a different ligand, CA19-9 enhances metastasizing via a mechanism leading to extravascular invasion [31].

From a clinical point of view, this information may be of little practical use due to the dismal prognosis of PaC patients. In fact, while LC and DMFS rates were significantly different based on the CA19-9 classes defined in this study, their values were low in all cases. For example, in the class (5.1-37.0 U/ml) with lower incidence of disease recurrences, 5-year LC and DMFS were 63.3% and 46.0%, respectively. Therefore, these values cannot justify a deescalation of adjuvant therapies. However, this information suggests that it would be appropriate to stratify patients by presurgical CA19-9 values in future trials on PaC having LC and DMFS as end points. Finally, considering the significant impact of the presurgical value of this marker on both LC and metastases, new studies could be specifically designed for patients with presurgical CA19-9 >200 U/ml. These trials should provide an intensification of both systemic (for example, by combining CT with immunotherapy) and local treatments (for example, with a dose escalation of postoperative RT achievable using the most modern RT techniques).

Conclusion

Our pooled analysis showed that presurgical CA19-9 levels significantly predict OS, LC, and DMFS. Future researches in this field seem justified in order to test the possibility of increasing the predictive power of CA19-9 through a dynamic evaluation of its level and/or in association with other tumor biomarkers and/or together with radiomic analysis. Furthermore, our report suggests the inclusion of CA19-9 in predictive models and in patients' stratification in future trials on resectable PaC.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tranon.2018.08.017>.

Disclosure

The authors have no actual or potential conflicts of interest existing regarding this paper. The abstract has previously been presented as a poster at the 35th Annual meeting of the ESTRO (European Society for Radiotherapy & Oncology), Torino, Italy, April 29-May 2, 2016.

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