Original Article

Prognostic impact of carbohydrate antigen 19-9 level at diagnosis in resected stage I–III pancreatic adenocarcinoma: a U.S. population study

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Background: Pancreatic adenocarcinoma is a highly aggressive cancer, with surgical resection and systemic therapy offering the only hope for long-term survival. Carbohydrate antigen 19-9 (CA 19-9) has been used as a prognostic marker after resection; however, the relationship between survival and pre-treatment CA 19-9 level remains unclear. This study evaluates pre-treatment serum CA 19-9 level as a predictor for long-term survival.

Methods: The U.S. National Cancer Data Base [2004–2012] was reviewed for patients with clinical stages I–III resected pancreatic adenocarcinoma with recorded pre-treatment CA 19-9 levels (U/mL). Kaplan Meier and Weibull survival analyses were performed.

Results: Four thousand seven hundred and one patients were included: 12.6% received neoadjuvant therapy (NAT), 27.4% underwent surgery, and 60.1% underwent surgery and adjuvant therapy. Amongst those who underwent initial surgery, there was no association between CA 19-9 levels ≤800 (≤100, 101–300, 301–500, 501–800) with survival (stage I P=0.7592, stage II P=0.5088, stage III P=0.9037). Levels >800 were associated with significantly worse survival in all stages (P≤0.0001, all). Amongst those who received NAT, levels >800 were associated with worse survival in early (stage I P=0.0001), but not advanced stage disease (stage II P=0.1891, stage III P=0.9316). In multivariable analyses, levels >800 demonstrated a 3.29 greater hazard of mortality with respect to patients with levels ≤100 (P<0.0001).

Conclusions: Pre-treatment CA 19-9 levels >800 appear to be associated with advanced disease, and are negatively associated with long-term survival. However, levels ≤800 had no significant association with survival. Although this study suggests an association, further study is needed to evaluate whether patients with CA 19-9 levels >800 benefit from NAT.

Keywords: Pancreatic cancer; carbohydrate antigen 19-9 (CA 19-9)

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Introduction

Pancreatic adenocarcinoma is a highly aggressive cancer, with surgical resection and systemic therapy offering the only hope for long-term survival. Due to its anatomical location, the majority of patients present with advanced disease, with only 15–20% presenting as surgical candidates (1). Thus, there is a tremendous demand for prognostic markers.

One such marker is carbohydrate antigen 19-9 (CA 19-9), a sialylated Lewis blood group antigen regarded to be the most sensitive and specific serum marker for pancreatic

cancer to date (2-4). While a CA 19-9 level of 37 U/mL is regarded as normal, a wide array of non-malignant elevators make the tumor marker a poor screening test in asymptomatic patients (5,6). CA 19-9 has been used as a prognostic marker after resection to monitor for recurrence and as a prognostic factor in inoperable cancer (7,8). However, correlation of CA 19-9 level at diagnosis with survival in resectable pancreatic cancer remains unclear. This study evaluates serum CA 19-9 level prior to treatment as a predictor for long-term survival.

Methods

Data

The National Cancer Data Base (NCDB) is a clinical oncology database based on hospital registry data in the United States. The data reflects over 70% of newly diagnosed cancer cases [1998–2012] from over 1,500 Commission on Cancer accredited facilities. This was a retrospective cohort study of clinical data from this registry from 2004–2012. The study was deemed exempt by the M. S. Hershey Medical Center Human Subject Protection Board and it conforms to the provisions of in accordance with the Helsinski Declaration as revised in 2013, available at: http://www.wma.net/en/30publications/10policies/b3/%20index.html.

Patient selection

The NCDB was reviewed for patients diagnosed with clinical stages I–III resected pancreatic adenocarcinoma with CA 19-9 levels prior to treatment recorded. Patients with clinical stage IV disease or unknown stage were excluded. Clinical stage is a coded variable within the NCDB which is determined per individual institution. Histologies included in this analysis were carcinoma and adenocarcinoma identified using the third edition of the *International Classification of Diseases for Oncology* (ICD-O-3) primary site codes: C250–C254, C257–C259 and histology ICD-O-3 codes: 8050/3 8140/3, 8144/3, 8148/3, 8160/3, 8230/3, 8255/3, 2890/3, 8310/3, 8323/3, 8342/3, 8346/3, 8380/3, 8430/3, 8460/3, 8461/3, 8480/3, 8481/3, 8500/3, 8503/3, 8504/3, 8507/3, 8510/3, 8521/3, 8523/3, 8550/3, 8560/3, 8562/3, 8570/3, 8574/3, and 8576/3. Patients who underwent an unknown surgical procedure, or local excision of tumor were excluded, in order to best capture those patients undergoing formal pancreatic resection. Patients with missing or unknown CA 19-9 levels were excluded. In the NCDB, CA 19-9 level is coded as 0–980 U/mL, with values over 980 U/mL coded simply as ≥980 U/mL.

Outcomes and covariates

The primary outcome assessed was survival from diagnosis. The highest CA 19-9 lab value documented in the medical record prior to treatment was coded with the database. In order to best capture patients with malignancy related elevations in CA 19-9, the study population was stratified at a CA 19-9 level of 800 U/mL. Covariates included sex, race, age, median income, insurance type and the Charlson/Deyo comorbidity index (CCI). The CCI is an index of 15 common comorbidities including ranging from cardiac to pulmonary, to vascular, to renal, to endocrine disorders (9,10).

Treatment facilities were characterized by geographic region and facility type. Disease was characterized by clinical and pathological variables including the American Joint Committee on Cancer (AJCC) clinical stage, number of lymph nodes sampled, number of positive lymph nodes, surgical margins, and pathological stage. Treatment was characterized by surgery type (distal pancreatectomy, whipple, total pancreatectomy and other), neoadjuvant treatment (NAT), and adjuvant treatment.

Statistical analysis

STATA software (version 12.1, StataCorp., College Station, TX, USA) was used to perform statistical analyses. Patient, disease, and treatment characteristics were compared between groups using student's *t*-tests, and chi square tests, as appropriate. Survival was assessed with Kaplan-Meier analyses stratified by CA 19-9 categories and a Weibull model.

Results

Of the 4,701 patients with clinically staged I–III resected pancreatic adenocarcinoma, 592 (12.6%) received neoadjuvant therapy, 1,286 (27.4%) underwent surgical resection alone, and 2,823 (60.1%) underwent surgery followed by adjuvant therapy. The median CA 19-9 level was 888 U/mL (range, 0–980 U/mL), with a distribution demonstrating 19.9% with CA 19-9 levels ≤100 U/mL, 12.2% between 100 and 300 U/mL, 6.6% between 300 and 500 U/mL, 7.1% between 500 and 800 U/mL, and 54.2% >800 U/mL (*Figure 1*).

Patient demographics stratified by treatment and

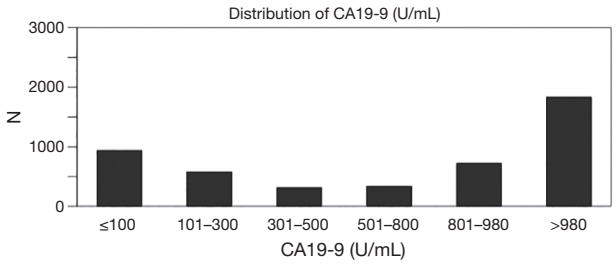

Figure 1 Distribution of CA 19-9 levels. CA 19-9, carbohydrate antigen 19-9.

CA 19-9 levels ≤800 and >800 U/mL are reported in *Table 1*. Within the cohort of patients who underwent surgical resection alone or received adjuvant therapy, patients with CA 19-9 levels ≤800 U/mL were younger (66.0 *vs.* 66.8, P=0.0174), and non-white (23.4% *vs.* 21.3%, P=0.002) with respect to patients with CA 19-9 levels ≤800 U/mL. Within the cohort of patients who received neoadjuvant therapy, patients with CA 19-9 levels ≤800 U/mL tended to be non-white (25.0% *vs.* 14.3%, P=0.007), but there was no difference in age (P=0.326) or sex (P=0.409).

Disease and treatment characteristics within the two cohorts are presented in *Table 2*. Among patients who underwent surgery with or without adjuvant therapy, those with CA 19-9 levels >800 U/mL tended to have higher clinically staged disease (P=0.001) and pathologically staged disease (P<0.0001) relative to patients with CA 19-9 levels ≤800 U/mL. They were more likely to undergo a pancreaticoduodenectomy (P<0.001), have positive surgical margins (P<0.0001), greater numbers of positive regional lymph nodes (P<0.0001), and were less likely to receive adjuvant therapy (P<0.0001). Among patients who received neoadjuvant therapy, there was no statistically significant difference in clinical or pathological stage, surgical margins, or positive number of lymph nodes between patients with CA 19-9 levels ≤800 U/mL and >800 U/mL.

Kaplan-Meier survival analyses for patients who underwent surgical resection with or without adjuvant therapy are presented in *Figure 2*. There was no association of CA 19-9 levels ≤800 U/mL with survival at any stage (stage I P=0.7592, stage II P=0.5088, stage III P=0.9037). CA 19-9 levels >800 U/mL were associated with significantly worse survival in all clinical stages of disease (stage I P<0.0001, stage II P<0.0001, stage III P<0.0001) (*Figure 3*).

Kaplan-Meier survival analyses for patients who received neoadjuvant therapy followed by surgical resection are presented in *Figure 4*. There was no association of CA 19-9 levels ≤800 U/mL with survival in early stage disease (stage I P=0.3030, stage II P=0.2908). While there was a statistically significant difference in survival among CA 19-9 levels below 800 in stage III disease (P=0.0464), this analysis was limited by small sample size (n=35). CA 19-9 levels >800 U/mL were associated with significantly worse survival in stage I disease (P=0.0001), but not in stage II or III disease (P=0.2029, P=0.9215, respectively) (*Figure 5*).

After controlling for patient, disease, and treatment characteristics, patients who received neoadjuvant or adjuvant therapy had a lower hazard of mortality relative to patients who underwent surgical resection alone (HR 0.60, P<0.001, HR 0.52, P<0.001) (*Table 3*). Patients with CA 19-9 levels 801–980 U/mL or >980 U/mL had significantly greater hazards of mortality relative to patients with CA 19-9 levels ≤100 U/mL (HR 3.29, P<0.001, HR 1.51, P<0.001, respectively).

Discussion

While a CA 19-9 level of 37 U/mL is widely regarded as normal, there are varying reports of levels associated with malignancy prognosis (5). This study found an association between pre-treatment CA 19-9 levels >800 U/mL and advanced stage disease. A CA 19-9 level >800 U/mL was associated with worse survival in all clinical stages of disease, and was found to be an independent poor prognostic factor. Some have used CA 19-9 levels to characterize resectability. A study of 244 patients with pancreatic adenocarcinoma, reported a 70% R0 resection in patients with both negative preoperative CA 19-9 and CEA levels (11). A number of small single institution studies have evaluated the predictive value of CA 19-9 levels in resectability. The CA 19-9 level reported as predictive of resectability has ranged from 92.8 to 622 U/mL (11-14). To our knowledge, this is the first study to evaluate the prognostic impact of a wide range of CA 19-9 levels.

In this study, neoadjuvant therapy was associated with a survival benefit in patients with CA 19-9 levels >800 U/mL. A broad study by Bergquist *et al.* evaluating patients with stage I and II disease, reported that though elevations in CA 19-9 levels >37 U/mL were associated with poorer survival, administration of neoadjuvant chemotherapy mitigated this effect (15). While surgery and systemic adjuvant therapy are standard of care, as few as half may actually receive intended adjuvant therapy (16,17). In this study, nearly one third underwent surgical resection, but received no form of systemic therapy. Receipt of neoadjuvant therapy has been

Table 1 Patient demographics

Variables	Surgery +/– adjuvant therapy			Neoadjuvant therapy		
	≤800 (n=1,907)	>800 (n=2,223)	P value	≤800 (n=256)	>800 (n=336)	P value
Age	66.0	66.8	0.0174	63.4	64.2	0.326
18–59	27.2%	23.5%		36.7%	31.8%	
60–69	32.2%	33.7%		34.5%	36.4%	
70–79	31.4%	32.1%		24.2%	25.5%	
80–90	9.3%	10.7%		4.5%	6.3%	
Sex			0.893			0.409
Male	51.2%	51.4%		47.3%	50.7%	
Female	48.8%	48.6%		52.7%	49.3%	
Race			0.002			0.007
White (Non-Hispanic)	76.6%	78.7%		75.0%	85.7%	
Black (Non-Hispanic)	11.1%	7.8%		14.4%	8.3%	
Other (Non-Hispanic)	3.5%	3.2%		3.4%	1.1%	
Hispanic	8.8%	10.3%		7.2%	4.9%	
Insurance			0.013			0.009
Private	34.8%	34.3%		45.1%	46.4%	
Medicare	54.0%	54.7%		41.7%	46.7%	
Medicaid & other gov	7.2%	5.7%		9.5%	3.7%	
Unknown	1.2%	2.4%		1.9%	0.3%	
Not insured	2.8%	2.8%		1.9%	2.9%	
Median income			0.093			0.004
<58,000	17.4%	15.0%		17.4%	12.3%	
58,000–74,000	23.5%	23.6%		26.1%	19.5%	
74,000–93,000	24.2%	26.7%		21.2%	33.2%	
>93,000	32.5%	31.0%		32.6%	30.1%	
Comorbidities			0.072			0.216
CDCC score 0	67.0%	63.7%		68.2%	62.8%	
CDCC score 1	26.3%	28.4%		26.5%	33.0%	
CDCC score 2	6.7%	7.9%		5.3%	4.3%	
CDCC score missing	0.0%	0.0%		0.0%	0.0%	
Facility type			0.412			0.772
Community	4.0%	4.1%		1.9%	1.4%	
Comprehensive community	38.9%	40.8%		29.5%	31.8%	
Academic/research	56.8%	55.0%		68.6%	66.8%	
Other	0.4%	0.2%		0.0%	0.0%	
Facility location			0.031			0.333
Northeast	21.6%	18.4%		22.0%	28.4%	
South	35.6%	35.1%		34.8%	31.5%	
Midwest	27.8%	30.1%		31.8%	28.7%	
West	15.0%	16.4%		11.4%	11.5%	

Table 2 Disease and treatment characteristics

Variables	Surgery +/– adjuvant therapy			Neoadjuvant therapy		
	≤800 (n=1,907)	>800 (n=2,223)	P value	≤800 (n=256)	>800 (n=336)	P value
Clinical stage			0.001			0.059
Stage I	44.8%	40.5%		27.7%	22.6%	
Stage II	51.5%	55.0%		59.1%	57.3%	
Stage III	2.9%	4.3%		13.3%	20.1%	
Surgery type			<0.0001			0.682
Distal resection	16.2%	11.6%		11.4%	8.9%	
Whipple	51.0%	54.8%		53.8%	55.6%	
Total resection	12.5%	12.2%		14.4%	16.3%	
Other	20.3%	21.4%		20.5%	19.2%	
Regional lymph nodes sampled	16.2	16.7	0.158	17.1	14.2	0.011
Positive regional lymph nodes	2.2	3.0	<0.0001	1.2	1.1	0.754
Surgical margins			<0.0001			0.855
No residual tumor	76.0%	70.0%		81.1%	78.5%	
Residual tumor, NOS	8.4%	9.5%		8.0%	7.7%	
Microscopic residual tumor	12.5%	15.4%		7.2%	8.6%	
Macroscopic residual tumor	0.9%	1.2%		0.4%	0.9%	
Indeterminate or unknown	2.3%	4.0%		3.4%	4.3%	
Pathological stage			<0.0001			0.058
Stage 0	0.4%	0.2%		0.8%	0.6%	
Stage 1	12.1%	7.1%		21.2%	18.3%	
Stage 2	75.5%	76.8%		61.0%	59.0%	
Stage 3	2.3%	4.3%		3.0%	3.7%	
Stage 4	1.7%	1.7%		0.0%	2.6%	
Unknown	5.2%	7.2%		9.1%	12.6%	
Treatment			<0.0001			1.000
Any NAT	0.0%	0.0%		100.0%	100.0%	
Surgery only	26.9%	35.1%		0.0%	0.0%	
Any adj	73.1%	64.9%		0.0%	0.0%	

NOS, not otherwise specified; NAT, neoadjuvant therapy; adj, adjuvant therapy.

associated with survival benefits in advanced pancreatic cancer, and appears to offer survival benefits in patients with elevated CA 19-9 (18,19). Elevations in the biomarker, particularly >800 U/mL should prompt clinicians to consider neoadjuvant therapy.

To our knowledge, this is the largest and most contemporary analysis of CA 19-9 levels at diagnosis of pancreatic adenocarcinoma, and the only to examine the impact of CA 19-9 elevations at multiple levels in resectable pancreatic cancer. However, there are some important limitations which should be acknowledged, including those inherent to retrospective reviews of large databases.

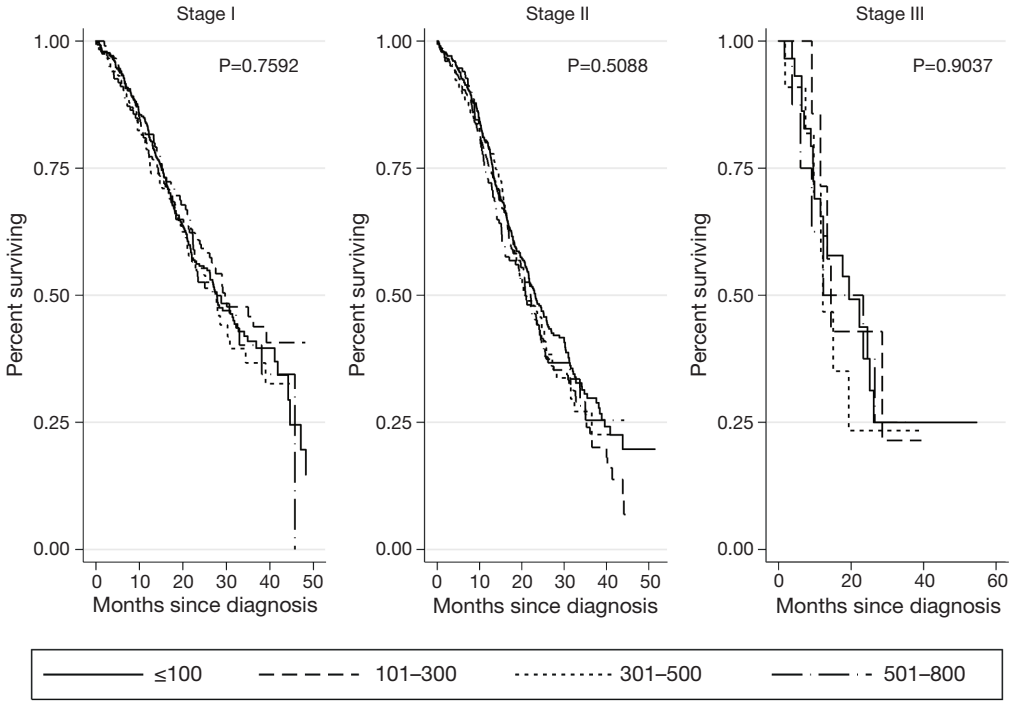

Figure 2 Kaplan Meier analyses for patients who underwent surgery +/– adjuvant therapy by CA 19-9 level (U/mL). CA 19-9, carbohydrate antigen 19-9.

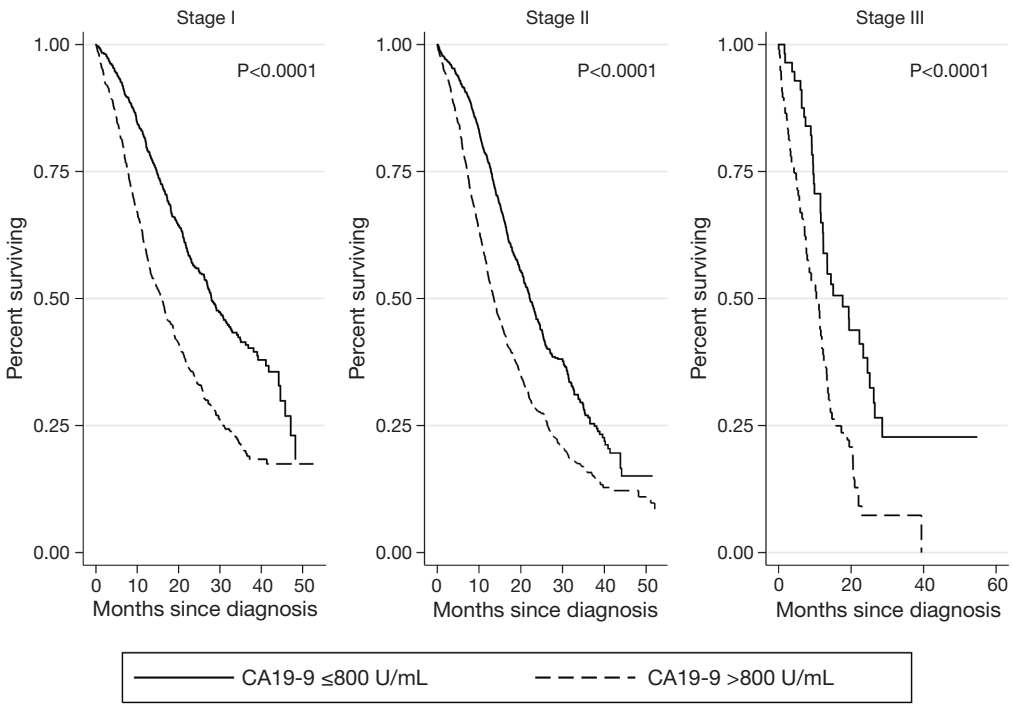

Figure 3 Kaplan Meier analyses for patients who underwent surgery +/– adjuvant therapy by CA 19-9 level (U/mL). CA 19-9, carbohydrate antigen 19-9.

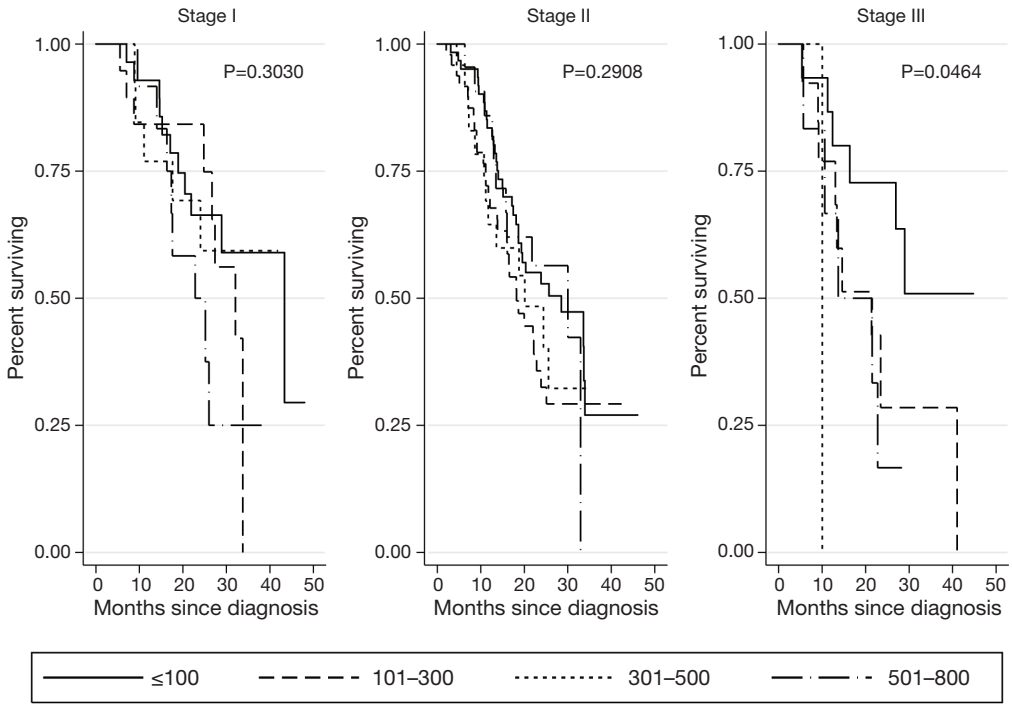

Figure 4 Kaplan Meier analyses for patients who received neoadjuvant therapy followed by surgery, by CA 19-9 level (U/mL). CA 19-9, carbohydrate antigen 19-9.

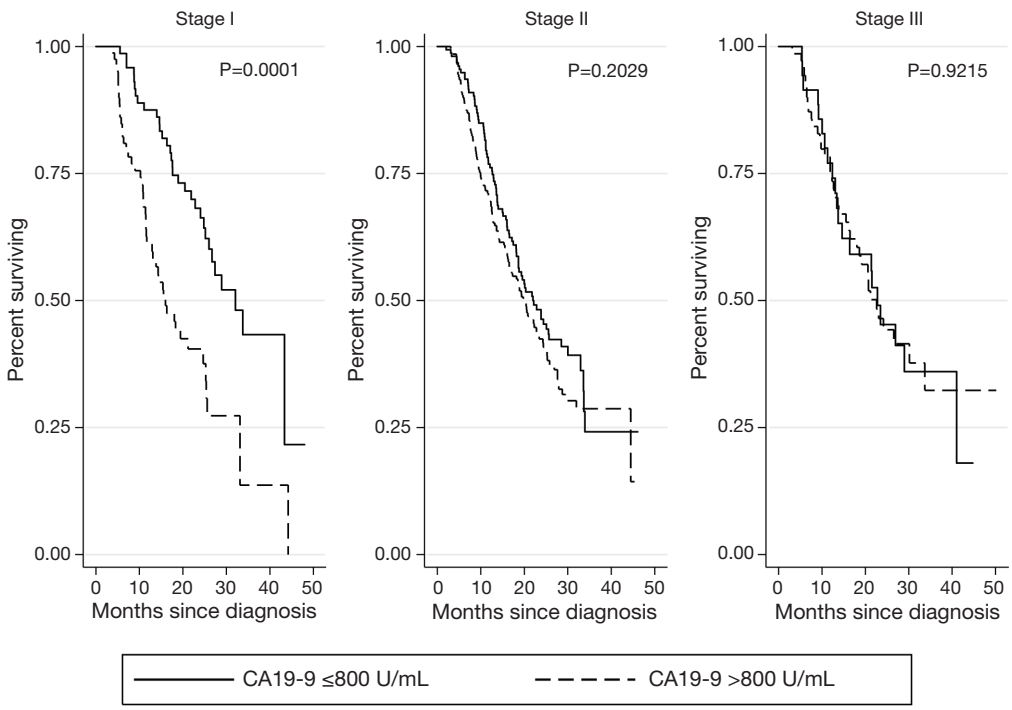

Figure 5 Kaplan Meier analyses for patients who received neoadjuvant therapy followed by surgery, by CA 19-9 level (U/mL). CA 19-9, carbohydrate antigen 19-9.

Table 3 Multivariate survival analysis

Variables	Coefficient	95% confidence interval		P value
		Lower	Upper	
Treatment				
Surgery	Reference			
Neoadjuvant	0.60	0.53	0.68	<0.001
Adjuvant	0.52	0.48	0.56	<0.001
Age (years)				
18–59	Reference			
60–69	1.12	1.00	1.25	0.043
70–79	1.23	1.08	1.40	0.001
80–90	1.35	1.15	1.59	<0.001
Sex				
Male	Reference			
Female	0.96	0.89	1.04	0.309
Race				
White	Reference			
Black	0.89	0.83	1.37	0.606
Other	0.89	0.79	0.99	0.033
Hispanic	1.00	0.80	1.00	0.050
Insurance				
Medicare	Reference			
Private	0.91	0.82	1.01	0.065
Medicaid & other gov	1.01	0.86	1.20	0.866
Unknown	0.40	0.29	0.55	<0.001
Not Insured	1.07	0.83	1.37	0.606
Median income				
<58,000	Reference			
58,000–74,000	0.88	0.79	0.99	0.033
74,000–93,000	0.89	0.80	1.00	0.050
>93,000	0.81	0.72	0.91	<0.001
Comorbidities				
CDCC score 0	Reference			
CDCC score 1	1.03	0.95	1.12	0.462
CDCC score 2	1.24	1.08	1.43	0.002

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Coefficient	95% confidence interval		P value
		Lower	Upper	
Facility type				
Community	Reference			
Comprehensive community	0.91	0.75	1.09	0.301
Academic/research	0.79	0.65	0.95	0.013
Other	1.54	0.75	3.18	0.243
Facility location				
Northeast	Reference			
South	1.04	0.93	1.16	0.501
Midwest	1.12	1.00	1.25	0.046
West	0.87	0.76	0.99	0.036
Surgery type				
Distal resection	Reference			
Whipple	1.17	1.04	1.32	0.010
Total resection	1.10	0.95	1.28	0.203
Other	1.10	0.96	1.26	0.171
Surgical margins				
No residual tumor	Reference			
Residual tumor, NOS	1.57	1.39	1.78	<0.001
Microscopic residual tumor	1.62	1.46	1.80	<0.001
Macroscopic residual tumor	1.50	1.06	2.11	0.021
Indeterminate or unknown	1.16	0.94	1.43	0.177
Pathological stage				
Stage 0	Reference			
Stage 1	0.66	0.51	0.86	0.002
Stage 2	1.08	0.86	1.35	0.521
Stage 3	1.24	0.92	1.66	0.153
Stage 4	1.91	1.37	2.68	<0.001
Unknown	1.08	0.83	1.41	0.556
CA 19-9 (U/mL)				
≤100	Reference			
101–300	1.10	0.95	1.27	0.184
301–500	1.08	0.90	1.29	0.393
501–800	1.08	0.91	1.28	0.409
801–980	3.29	2.89	3.74	<0.001
>980	1.51	1.36	1.69	<0.001

NOS, not otherwise specified.

The NCDB codes only for the highest CA 19-9 value documented in the medical record prior to treatment. These values are derived from a heterogenous population of hospitals with non-uniform biomarker assays. Additionally, the NCDB does not code for potential confounders of CA 19-9 elevation such as PPI use, or biliary obstruction. Given the retrospective nature of the study, the treatment cohorts likely contain a selection bias.

Conclusions

An elevated CA 19-9 level >800 U/mL appears to be associated with more advanced stage disease; however, CA 19-9 ≤800 drawn prior to treatment had no significant association with long-term survival. CA 19-9 levels >800 U/mL were negatively associated with long-term survival. Although this study suggests an association, further study is needed to evaluate whether patients with CA 19-9 levels > 800 U/mL benefit from NAT.

Acknowledgements

None.

Footnote

Conflicts of Interest: This study was selected and presented as a poster presentation at the European Society of Medical Oncology 18th World Congress on Gastrointestinal Cancer, June 29–July 2, 2016, Barcelona, Spain.

Ethical Statement: The study was deemed exempt by the M. S. Hershey Medical Center Human Subject Protection Board and it conforms to the provisions of in accordance with the Helsinski Declaration as revised in 2013, available at: http://www.wma.net/en/30publications/10policies/b3/%20index.html.

Disclaimer: The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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