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The prognostic and predictive value of serum CA19.9 in pancreatic cancer

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Background: Current staging methods for pancreatic cancer (PC) are inadequate, and biomarkers to aid clinical decision making are lacking. Despite the availability of the serum marker carbohydrate antigen 19.9 (CA19.9) for over two decades, its precise role in the management of PC is yet to be defined, and as a consequence, it is not widely used.
Methods: We assessed the relationship between perioperative serum CA19.9 levels, survival and adjuvant chemotherapeutic responsiveness in a cohort of 260 patients who underwent operative resection for PC.
Results: By specifically assessing the subgroup of patients with detectable CA19.9, we identified potential utility at key clinical decision points. Low postoperative CA19.9 at 3 months (median survival 25.6 vs 14.8 months, $P = 0.0052$) and before adjuvant chemotherapy were independent prognostic factors. Patients with postoperative CA 19.9 levels >90 U/ml did not benefit from adjuvant chemotherapy ($P = 0.7194$) compared with those with a CA19.9 of ≤ 90 U/ml (median 26.0 vs 16.7 months, $P = 0.0108$). Normalization of CA19.9 within 6 months of resection was also an independent favorable prognostic factor (median 29.9 vs 14.8 months, $P = 0.0004$) and normal perioperative CA19.9 levels identified a good prognostic group, which was associated with a 5-year survival of 42%.
Conclusions: Perioperative serum CA19.9 measurements are informative in patients with detectable CA19.9 (defined by serum levels of >5 U/ml) and have potential clinical utility in predicting outcome and response to adjuvant chemotherapy. Future clinical trials should prioritize incorporation of CA19.9 measurement at key decision points to prospectively validate these findings and facilitate implementation.
Key words: adjuvant chemotherapy, CA19.9, pancreatic cancer, prognosis

introduction

Pancreatic cancer (PC) is one of the most lethal solid organ malignancies. Pancreatectomy offers the only potential for cure but is only possible in a minority of patients. Even in those patients who undergo resection, most die because occult extrapancreatic metastatic disease was likely present at the time of diagnosis [1]. Systemic therapies are only modestly effective in advanced disease but have a significant impact in the adjuvant setting, with 5-fluorouracil and gemcitabine both having efficacy in a subgroup of patients and increasing 5-year survival from 10%–15% with surgery alone to 20%–25% [2–5]. As a consequence, there is an urgent need to develop biomarkers to better stratify patients for current treatment modalities and for the testing of novel therapeutic strategies. Carbohydrate antigen 19.9 (CA19.9), first isolated in 1979 [6, 7], is the only available serum biomarker for PC and has shown some utility as a diagnostic adjunct and a prognostic marker [8] but is not widely used in routine clinical practice [9]. Serum biomarkers such as prostate-specific antigen (PSA) in prostate cancer, carcinoembryonic antigen (CEA) in colorectal cancer and CA 125 in ovarian cancer, which have similar limitations and although sometimes controversial are routinely used and are an integral component of clinical trials in those diseases.

Defining the subgroup of individuals where CA19.9 measurement is robust in predicting prognosis and

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chemotherapeutic responsiveness for PC would improve current management and overall outcomes. Here, we show that serum CA19.9 has distinct potential clinical utility in PC patients when assessed at distinct clinical decision points along the patient journey.

patients and methods

Detailed clinicopathologic and outcome data were collected for 260 consecutive patients who had a histopathologic diagnosis of pancreatic ductal adenocarcinoma and recorded CA19.9 levels from hospitals associated with the New South Wales Pancreatic Cancer Network, Australia (NSWPCN; www.pancreaticcancer.net.au), as previously described [10, 11]. This cohort of patients was retrospectively and then prospectively recruited when the database was established in 1999. The censor date was 30 September 2010. Ethical approval for the acquisition of data and biological material was obtained from the Human Research Ethics Committee at each participating institution. Clinical data were obtained from patients and family members, hospital notes and physician records. Outcome data including the date and cause of death were sourced from the NSW Cancer Registry and treating clinicians.

Survival was measured from the date of histopathologic diagnosis until date of death or last follow-up. Patients with an R2 resection (macroscopically positive resection margins) were excluded from the analysis. All patients were staged based on the American Joint Committee on Cancer (AJCC) TNM (tumor–node–metastasis) classification, 7th edition [12]. Recurrence was defined by pathological confirmation by biopsy, cytology or clinical and radiographic findings consistent with metastatic disease.

CA19.9 measurement

CA19.9 measurements were carried out at certified laboratories associated with the hospital where the patients were treated. The upper limit of normal used for CA19.9 was 37 U/ml. Red cell phenotyping for Lewis antigen status was not carried out in the majority of patients; therefore, patients whose CA19.9 levels were persistently <5 (termed non-expressors) were deemed likely to be Lewis antigen (Le^{a-b-}) negative and were analyzed as a separate group. Paired bilirubin and liver enzymes levels were also collected. CA19.9 levels may be artificially elevated in the setting of cholestasis and correcting it in relation to the bilirubin may improve its applicability. Significant impairment in biliary excretion for which bilirubin is a surrogate marker occurs when the bilirubin level is >1.5 times the upper limit of normal (or >2 mg/dl) [13]. Analyses were carried out using CA19.9 values in patients with normal bilirubin levels and in those with impaired biliary excretion (bilirubin > 2 mg/dl). In patients with bilirubin >2 mg/dl, the corrected CA19.9 (cCA19.9) was calculated by dividing the CA19.9 value by the bilirubin (in mg/dl) [13–15].

patient cohort

The cohort consisted of 260 consecutive patients who had a pathological diagnosis of pancreatic ductal adenocarcinoma who underwent pancreatic resection with curative intent (macroscopically clear margins). The clinicopathologic characteristics are summarized in supplementary TableS1 (available at *Annals of Oncology* online). Clinico-pathologic factors associated with significantly better survival on univariate analysis (Table 1) included tumors of the pancreatic head (median survival 20.7 versus 11.9 months; $P = 0.0053$) compared with those of the body/tail, tumor size ≤ 20 mm (34.4 versus 16.7 months; $P = 0.0019$), absence of margin involvement (22.8 versus 13.2 months; $P = 0.0002$), absence of lymph node metastases (22.2 versus 16.8 months; $P = 0.0261$), and adjuvant chemotherapy (22.4 versus 16.7 months; $P = 0.0029$).

Table 1. Descriptive statistics for patients resected for PC with CA19.9 values ($n = 260$)

Parameter	Resected patients with CA19.9 values		
	$N = 260$, No. (%)	Median DSS (months)	P value (log-rank)
Sex			
Female	123 (47.3)	18.1	0.9721
Male	137 (52.7)	19.4	
Age, y			
Mean	65.9		
Median (range)	67.0 (28–87)		
Outcome			
Follow-up (mo)	0–115.3		
Median follow-up	11.7		
30-day mortality	3 (1.2)		
Death PC	148 (56.9)		
Death other	17 (6.5)		
Alive	95 (36.5)		
Lost to follow-up	0		
Stage[a]			
IA	7 (2.7)	25.2	
IB	10 (3.8)	56.6	
IIA	68 (26.2)	22.2	
IIB	160 (61.5)	16.9	0.3121[b]
III	0	—	
IV	15 (5.8)	9.3	0.0002[c]
Differentiation[d]			
Well	23 (8.8)	22.8	0.8527
Moderate	163 (62.7)	18.1	
Poor	72 (27.7)	18.6	
Missing	2 (0.8)		
Tumor location[e]			
Head	211 (81.2)	20.7	0.0053
Body/tail	49 (18.8)	11.9	
Tumor size[f]			
≤20 mm	44 (16.9)	34.4	0.0019
>20 mm	164 (63.1)	16.7	
Missing	52 (20)		
Margins			
Clear	152 (58.5)	22.8	0.0002
Involved	107 (41.2)	13.2	
Missing	1 (0.4)		
Lymph nodes			
Negative	89 (34.2)	22.2	0.0261
Positive	171 (65.8)	16.8	
Perineural invasion			
Negative	54 (20.8)	25.6	0.2122
Positive	197 (75.8)	16.8	
Missing	9 (3.5)		
Vascular invasion			
Negative	108 (41.5)	20.7	0.1455
Positive	115 (44.2)	17.8	
Missing	37 (14.2)		
Adjuvant Chemotherapy			
No adjuvant[g]	140 (53.8)	16.7	
Any adjuvant	120 (46.2)	22.4	0.0029
<3 cycles	35 (13.5)	16.2	
≥3 cycles	85 (32.7)	34.3	0.0051

Table 1. (*Continued*)

Parameter	Resected patients with CA19.9 values		
	N = 260, No. (%)	Median DSS (months)	*P* value (log-rank)
Median time to adjuvant chemotherapy (months)	1.8		
Chemotherapeutic agent			
Gemcitabine monotherapy	89		
Gemcitabine + 5-FU chemoradiation	13		
Gemcitabine + nab-paclitaxel	1		
5-FU monotherapy	6		
5-FU chemoradiation	8		
Missing	3		
Recurrence	166 (63.8)		
R0	92 (35.4)		
R1	74 (28.5)		
Median time to recurrence (mo)	9.6		
R0	12.1		
R1	8.0		
Palliative chemotherapy	42 (16.2)		
Radiotherapy			
No radiotherapy	222 (85.4)	18.3	
Any radiotherapy	38 (14.6)	19.8	0.6596[h]
Adjuvant	29 (11.2)		0.8894[i]
Palliative	10 (3.8)		
CA19.9			
Pre-resection	*N* = 202		
Median time pre, (mo)	0.4		
Post-resection <3/12	*N* = 131		
Median time post <3/12, (mo)	1.2		
Post-resection lowest <6/12	*N* = 162		
Median time post <6/12 (mo)	1.9		
Pre and post <3/12	*N* = 88		

[a]Staging based on AJCC TNM Staging System, 7th Edition, 2010.
[b]Stage I tumors versus stage II for survival analysis.
[c]Stage I and 2 tumors versus Stage III and IV for survival analysis.
[d]Well-differentiated and moderately differentiated tumors grouped together for survival analysis.
[e]Patients with tumors located in the head of the pancreas underwent Whipple pancreaticoduodenectomies, and those with tumors of the body/tail had left-sided pancreatectomies.
[f]Tumor size was also prognostic >30 mm ($P = 0.0015$), and >40 mm ($P < 0.0001$).
[g]Reasons for not receiving adjuvant chemotherapy: poor performance status, 18; patient declined, 14; physicians preference, 7; suspected/confirmed metastatic disease, 4; before 2004 (ESPAC-1 published in 2004 before this adjuvant chemotherapy was not universally accepted as the standard of care in Australia), 65; not documented post 2004, 32;
[h]Analysis compares those patients who received radiotherapy at any time to all others.
[i]Analysis compares those who received adjuvant radiotherapy versus those who did not.
CA19.9, carbohydrate antigen 19.9; DSS, disease-specific survival; PC, pancreatic cancer; 5-FU, 5-fluorouracil.

Pre-resection CA19.9 values were available in 202 patients and were taken a median of 0.4 months before surgery. Of these, 10 patients (5%) had CA19.9 levels <5 pre- and post-resection and in the absence of red cell phenotyping were deemed non-expressors. Post-resection CA19.9 values were available in 231 patients but only 131 and 162 patients had levels carried out within 3 and 6 months of surgery, respectively, and of these, 9 were excluded from the analysis due to being classified as non-expressors. Paired pre- and post-resection (within 3 months) CA19.9 values were available in 88 patients with 3 non-expressors excluded from the analysis.

Paired bilirubin assays at the time of CA19.9 measurement were available for all patients included in the analysis. Hyperbilirubinemia, defined as serum level greater than 1.5 times the upper limit of normal (>2 mg/dl or 34.2 μmol/l), was used as a marker of impaired biliary excretion. In the pre-resection group, the median bilirubin level was 2.0 mg/dL with hyperbilirubinemia present in 91 (45%). In the post-resection group, the median bilirubin level was 0.5 mg/dl with hyperbilirubinamia in eight (6%). In the paired pre- and post-resection group hyperbilirubinamia was present in 40 (45%) and 2 (2%), respectively.

statistical analysis

Median survival was estimated using the Kaplan–Meier method and the difference tested using the log-rank test. *P* values of <0.05 were considered statistically significant. Clinicopathologic variables analyzed with a significant *P* value and those reported to be significant were entered into a Cox Proportional Hazard multivariate analysis and models resolved using backward elimination of redundant variables. Statistical analysis was carried out using Statview 5.0 Software (Abacus Systems, Berkeley, CA). Disease-specific survival (DSS) was used as the primary end point.

results

Clinically relevant time points were examined to specifically assess a potential role in clinical decision making (ie at 3 months post-resection, within 6 months; before adjuvant therapy, and after adjuvant therapy). We initially assessed the value of post-resection CA19.9 in patients who produced CA19.9 (>5 U/ml) in relation to DSS and subsequently their response to adjuvant chemotherapy. In addition, we examined the potential value of preoperative CA19.9 and the change in level with surgery, with and without adjustment for hyperbilirubinamia.

prognostic value of CA19.9

post-resection CA19.9 and survival. Of the 122 patients with CA19.9 values at or within 3 months of surgery, the majority (114; 93%) had bilirubin levels <2 mg/dl and did not require CA19.9 adjustment. The post-resection CA19.9 cosegregated with DSS on univariate analysis into three prognostic groups: (i) those with <37 U/ml had the best outcome, (ii) 37–120 U/ml, an intermediate outcome, and (iii) >120 U/ml, the worst outcome (median 25.6 versus 20.7 versus 14.8 months, $P = 0.0052$; Figure 1A). In the 37–120 U/ml group, the CA19.9 decreased in five patients, normalized in three and increased in five patients at 6 months, suggesting that the intermediate group (37–120 U/ml) consisted of those that had elevated CA19.9 due to other causes as well as residual disease. Those within the normal range (<37 U/ml) within 6 months of resection had a better outcome (median 29.9 versus 14.8 months; $P = 0.0004$; Figure 1B).

post-resection CA19.9 and recurrence. Of the 122 patients with post-resection CA 19.9 values, 76 had pathologically clear

resection margins (R0), permitting assessment of disease-free survival (DFS). The median time to recurrence was 9.0 months (range 0.4–57). DFS paralleled DSS. Patients with a CA19.9 in the normal range within 3 months had significantly longer DFS than patients with CA19.9 >37 U/ml (median DFS 22.0 versus 11.5 months, $P = 0.0194$; Figure 1C).

pre-resection CA19.9 and survival. The ability to predict prognosis before pancreatectomy would significantly improve outcomes by better selecting patients for surgery. Preoperative measures of CA19.9 are often confounded by biliary obstruction, and as a consequence, we assessed if serum CA19.9 adjusted for hyperbilirubinamia could be used as a reliable measure of outcome. Of the 202 patients with available pre-resection CA19.9 values, 111 had paired bilirubin levels <2 mg/dl with a median CA19.9 of 138 U/ml (range 1–26 600). Those with a pre-resection CA19.9 <120 U/ml were associated with better DSS (median 35.6 vs 17.4, $P = 0.0444$; Figure 1D). In the remaining 91 patients with hyperbilirubinaemia, the median uncorrected and corrected CA19.9 was 351 and 28, respectively (range 1–101 075 and 0.1–16 780). Combined uncorrected and corrected pre-resection cCA19.9 <120 was also associated with a better DSS (22.2 versus 16.7, $P = 0.0058$; Figure 1E). Table 2 summarizes the univariate analysis for all categories of CA19.9 measurement. In

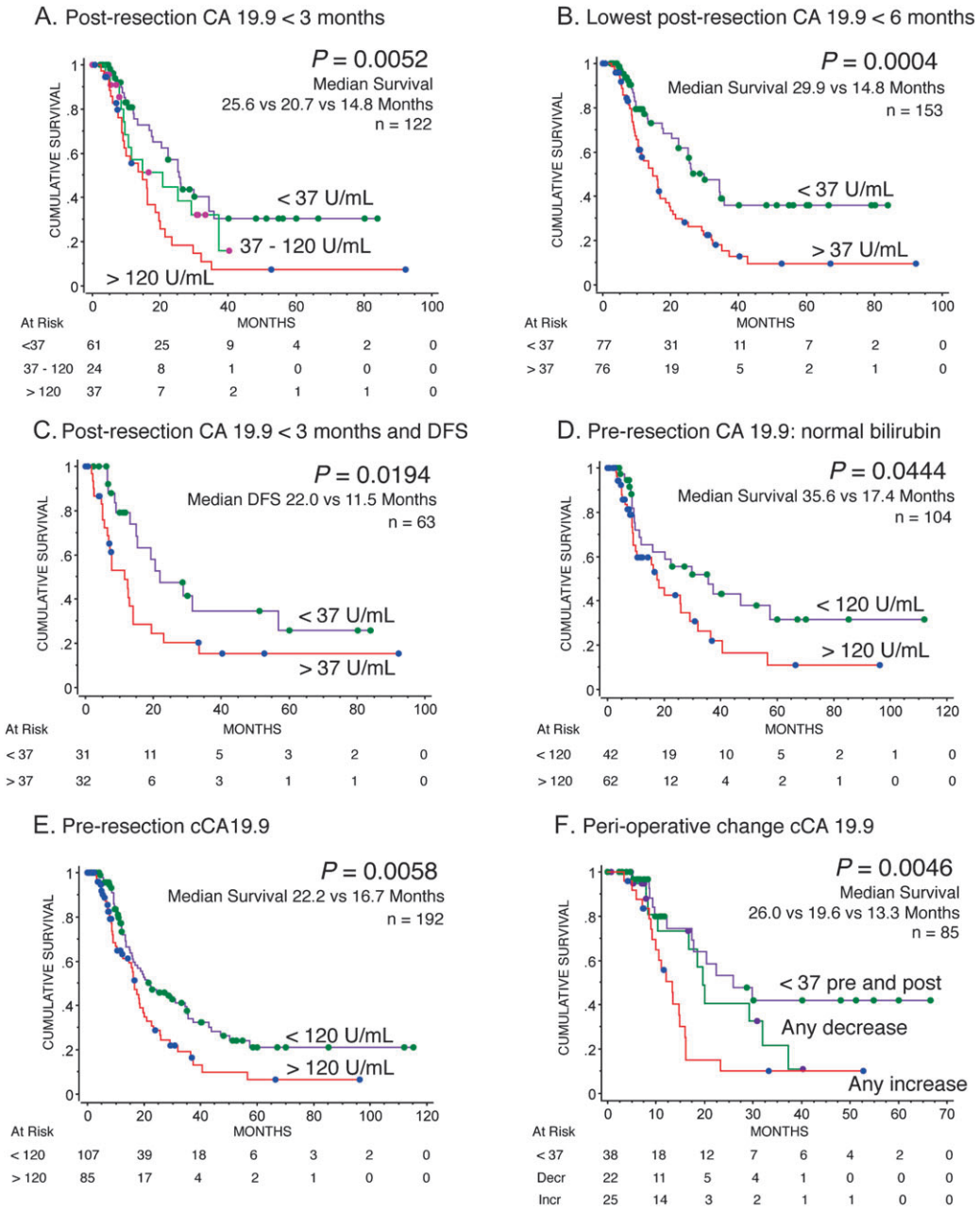

Figure 1. Kaplan–Meier survival curves for (A) Post-resection CA19.9 <3 months, (B) Lowest post-resection CA19.9 <6 months, (C) Post-resection CA19.9 <3 months and DFS, (D) Pre-resection CA19.9: normal bilirubin, (E) Pre-resection cCA19.9, (F) Perioperative change cCA19.9. CA19.9, carbohydrate antigen 19.9; cCA19.9, corrected CA19.9; DFS, disease-free survival.

addition, pre-resection CA19.9 was associated with pathological stage in patients with normal bilirubin levels but there was a wide range in CA19.9 values for each stage with overlap in the values between stages diminishing its clinical applicability (see Supplementary data, available at *Annals of Oncology* online).

perioperative change in CA19.9 and survival. Of the 85 patients with pre- and post-resection cCA19.9 values, the cCA19.9 level remained <37 U/ml (but >5) in 38 patients, decreased in 22 patients and increased in 25. These clustered into three corresponding prognostic groups: (i) <37 U/ml pre- and post-resection, (ii) a decrease in CA 19.9 and (iii) an increase in CA 19.9. Patients whose CA 19.9 was always in the normal range had a better survival compared with the CA 19.9 decrease and increase groups (median survival 26.0 versus 19.6 versus 13.3 months, $P = 0.0046$; Figure 1F; supplementary data, available at *Annals of Oncology* online).

multivariate analysis. A multivariate Cox proportional hazards model was developed using clinicopathologic variables with $P < 0.05$ and those reported to be prognostic on univariate analysis (Tables 1 and 2). The resolved multivariate model after removal of redundant variables showed that post-resection CA19.9 >120 U/ml, positive resection margins, and adjuvant chemotherapy were independent prognostic factors (Table 3).

predictive value of CA19.9

post-resection CA19.9 and benefit from adjuvant chemotherapy. Adjuvant chemotherapy was associated with better survival overall ($P = 0.0029$; Table 1); however, only patients with pre-adjuvant chemotherapy CA19.9 values <90 U/ml appeared to benefit. Of 71 patients with a post-resection CA19.9 <90 U/ml (measured within a month of commencement of adjuvant therapy or at an equivalent time point for surgery-only patients), 48 had adjuvant chemotherapy (45 received gemcitabine-based regimens). In these patients, adjuvant chemotherapy was associated with a significant survival benefit (median survival 26.0 versus 16.7 months, $P = 0.0108$; Figure 2A and C). There were 35 patients

Table 2. Univariate analysis of CA19.9 values at significant time points

Variable	Number	Median DSS (months)	*P* value (log-rank)
Prognostic			
Post-resection CA19.9 <3/12			
<37 U/ml	61	25.6	
37–120 U/ml	24	20.7	
>120 U/ml	37	14.8	0.0052
Post-resection CA19.9 <6/12			
<37 U/ml	77	29.9	
>37 U/ml	76	14.8	0.0004
Pre-resection CA19.9 (bilirubin <2 mg/dl)			
Non-expressors	10	18.6	
<120 U/ml	42	35.6	
>120 U/ml	62	17.4	0.0444
Pre-resection cCA19.9			
<120 U/ml	107	22.2	
>120 U/ml	85	16.7	0.0058
Peri-operative change cCA19.9			
<37 pre and post	38	26.0	
Any decrease	22	19.6	
Any increase	25	13.3	0.0046
Predictive			
Pre-adjuvant CA19.9			
<90 U/ml	48	26.0	
>90 U/ml	19	16.2	0.0190
Pre-adjuvant CA19.9 <90 U/ml			
Adjuvant chemotherapy	48	26.0	
No adjuvant chemotherapy	23	16.7	0.0108
Pre-adjuvant CA19.9 >90 U/ml			
Adjuvant chemotherapy	19	16.2	
No adjuvant chemotherapy	16	9.0	0.7194
Post-adjuvant CA19.9			
<37 U/ml	11	No patient died from PC	
>37 U/ml	8	19.6	Not calculable
Post-resection CA19.9 < 3/12—surgery alone			
<120 U/ml	40	20.7	
>120 U/ml	19	9.0	0.0628

CA19.9, carbohydrate antigen 19.9; PC, pancreatic cancer.

with post-resection CA19.9 >90 U/ml. Of these, 19 received adjuvant chemotherapy, with no statistically significant survival benefit (median survival 16.2 versus 9.0 months, $P = 0.7194$; Table 2 and Figure 2B, D and E). Multivariate analysis of variables within the CA19.9 <90 U/ml subgroup showed that adjuvant chemotherapy and size were independent prognostic factors with involved margins of borderline significance (Table 3). Although numbers were small, early data suggested that normal CA19.9 levels after completion of adjuvant therapy in those patients who produce CA19.9 may be associated with an excellent outcome (Figure 2F). At the censor date, all patients with post-chemotherapy CA19.9 >37 U/ml had developed metastatic disease. Two patients were alive with recurrences at 12 and 13 months, respectively, and the remainder had died of metastatic PC. Of those with post-chemotherapy CA19.9 <37 U/ml, 1 of the 11 patients had developed a recurrence with peritoneal involvement 48.9 months after the initial resection (41.6 months after completing chemotherapy).

discussion

Despite its acceptance as a measure of PC tumor burden, caveats in the interpretation of CA 19.9 values limit application across the full spectrum of PC. First, CA19.9 is a sialylated Lewis a (Le^a) antigen. Lewis antigens are normal components of exocrine epithelial secretions present on erythrocyte membranes formed from type I oligosaccharide precursors that undergo sequential addition of monosaccharides by a set of glycosyltransferases and fucosyltransferases [16]. Two independent genes determine the Lewis phenotype: the Lewis gene or α1-4 fucosyltransferase (also known as FUT3) and the secretor gene or α1-2 fucosyltransferase (FUT2) [17]. Individuals who lack a functional FUT3 allele are termed Lewis negative (Le^{a-b-}) and are unable to synthesize CA19.9 [18]. They comprise 7%–10% of Caucasians, but their incidence is higher in other populations such as Africans (22%) [17, 18]. Individuals with at least one functional FUT3 allele are characterized by the red cell phenotype Le^{a+b-} or Le^{a-b+} (rarely Le^{a+b+}). Lack of a functional FUT2 allele leads to the non-secretor phenotype (se/se), which is characterized by the absence of ABH determinants in saliva and on some epithelial cell types [16]. Non-secretors in general have higher serum and urine CA19.9 levels than secretors [19]. Second, CA 19.9 can also be elevated in benign pancreatic diseases such as pancreatitis [20], which often coexist with PC. Third, CA19.9 undergoes some degree of biliary excretion and is produced by biliary epithelial cells. Therefore, in the setting of cholestasis, CA19.9 levels are frequently elevated even in benign conditions [21].

Table 3. Multivariate analysis

Models	Variable	Hazard ratio (95% CI)	*P* value
Prognostic			
A. Resected PC with	Positive lymph nodes	1.69 (0.88–3.25)	0.1124
CA19.9, initial model ($n = 260$)	Size > 20 mm	1.45 (0.73–2.86)	0.2862
	Poorly differentiated	0.94 (0.47–1.85)	0.8466
	Vascular invasion	1.35 (0.71–2.54)	0.3596
	Perineural invasion	1.03 (0.54–1.97)	0.9203
	Involved margins	2.16 (1.12–4.15)	0.0207
	Adjuvant chemotherapy	0.65 (0.37–1.15)	0.1346
	Pre-resection cCA19.9 > 120 U/ml	1.27 (0.70–2.32)	0.4296
	Post-resection CA19.9 > 120 U/ml (≤3 months)	2.47 (1.37–4.44)	0.0026
B. Resected PC with	Positive lymph nodes	1.53 (0.99–2.35)	0.0553
CA19.9, resolved model ($n = 260$)	Size > 20 mm	1.61 (0.99–2.62)	0.0555
	Involved margins	1.79 (1.15–2.77)	0.0090
	Adjuvant chemotherapy	0.60 (0.39–0.92)	0.0198
	Post-resection CA19.9 > 120 U/ml (≤3 months)	1.87 (1.20–2.92)	0.0056
C. Resected PC with	Involved margins	2.19 (1.47–3.27)	0.0001
CA19.9, final model ($n = 260$)	Adjuvant chemotherapy	0.61 (0.40–0.91)	0.0172
	Post-resection CA19.9 > 120 U/ml (≤3 months)	1.90 (1.25–2.91)	0.0029
Predictive			
D. Pre-adjuvant CA19.9	Positive lymph nodes	1.09 (0.51–2.30)	0.8315
<90, initial model ($n = 78$)	Size > 20 mm	2.52 (1.15–5.52)	0.0209
	Poorly differentiated	1.11 (0.53–2.31)	0.7793
	Vascular invasion	1.09 (0.53–2.22)	0.8125
	Perineural invasion	2.20 (0.94–5.12)	0.0693
	Involved margins	1.69 (0.85–3.36)	0.1334
	Adjuvant chemotherapy	0.27 (0.13–0.55)	0.0004
E. Pre-adjuvant CA19.9	Size > 20 mm	2.56 (1.20–5.46)	0.0146
<90, resolved model ($n = 78$)	Involved margins	1.94 (1.00–3.79)	0.0509
	Adjuvant chemotherapy	0.28 (0.14–0.57)	0.0004

CA19.9, carbohydrate antigen 19.9; cCA19.9, corrected CA19.9; CI, confidence interval; PC, pancreatic cancer.

Serum CA19.9 possesses many features of a robust or clinically useful biomarker and has been well studied to define its limitations outlined above. Despite this, there are no clear applications for CA19.9 in the management of PC as there are for other similar serum biomarkers such as PSA for prostate cancer, CEA for colorectal cancer and CA 125 in ovarian cancer, which are although sometimes controversial, used in routine practice and form integral components of clinical trials to further advance clinical management. We focused on defining potential roles for serum CA19.9 at key clinical decision-making time points in patients who have demonstrable CA19.9 production. If an individual is identified to have the capacity to produce CA19.9, either through Lewis antigen testing or through a level over 5 U/ml at diagnosis as a surrogate, postoperative CA19.9 measurements have potential prognostic and predictive value. First, normalization of CA19.9 postoperatively is associated with a good prognosis. Second, postoperative CA19.9 levels >90 U/ml may be associated with a lack of response to adjuvant gemcitabine-based chemotherapy, and third, although numbers are small,

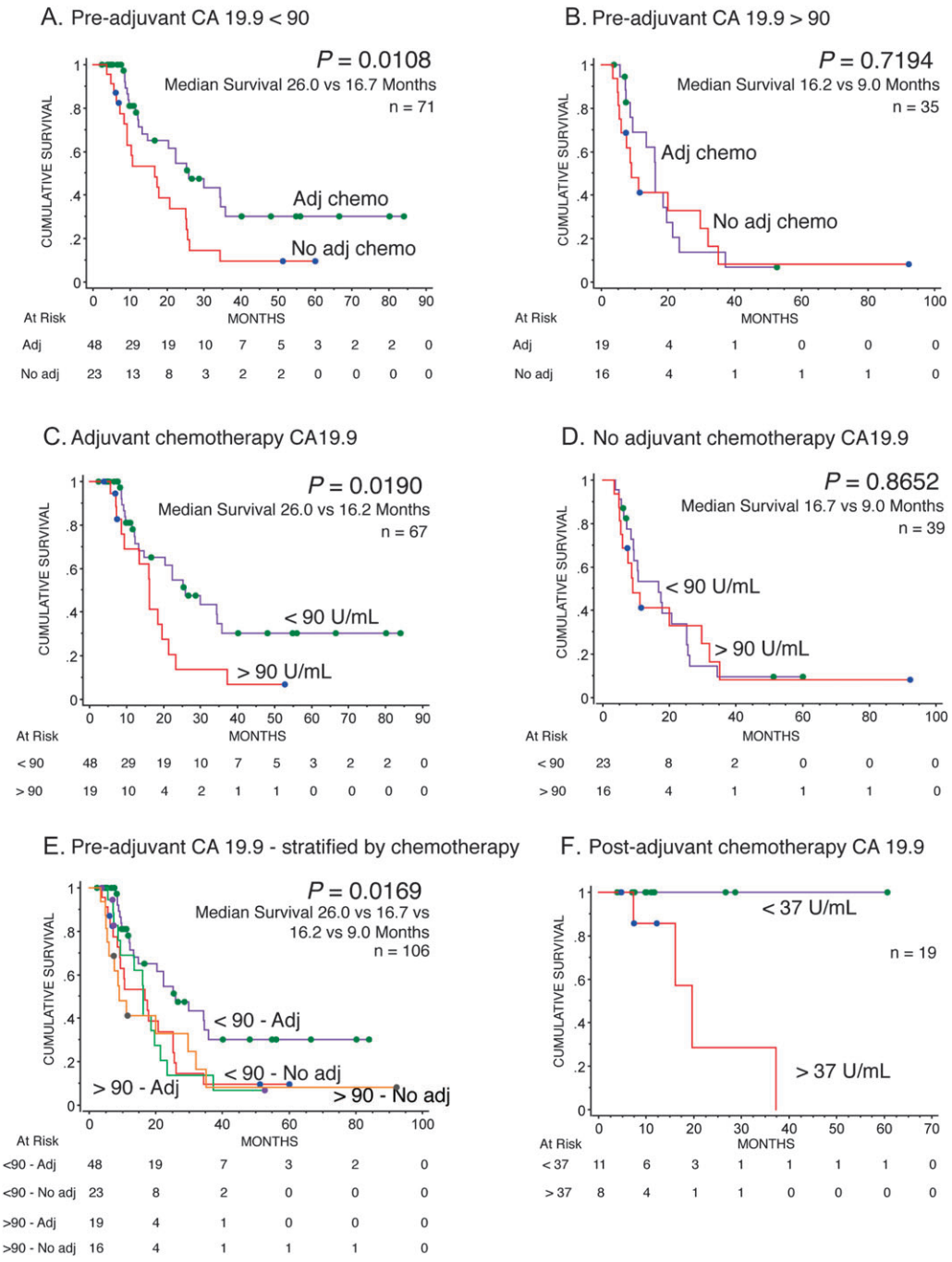

Figure 2. Kaplan–Meier survival curves for (A) Pre-adjuvant CA19.9 <90, (B) Pre-adjuvant CA19.9 >90, (C) Adjuvant chemotherapy CA19.9, (D) No adjuvant chemotherapy CA19.9, (E) Pre-adjuvant CA19.9—stratified by chemotherapy, (F) Post-adjuvant chemotherapy CA19.9. CA19.9, carbohydrate antigen 19.9.

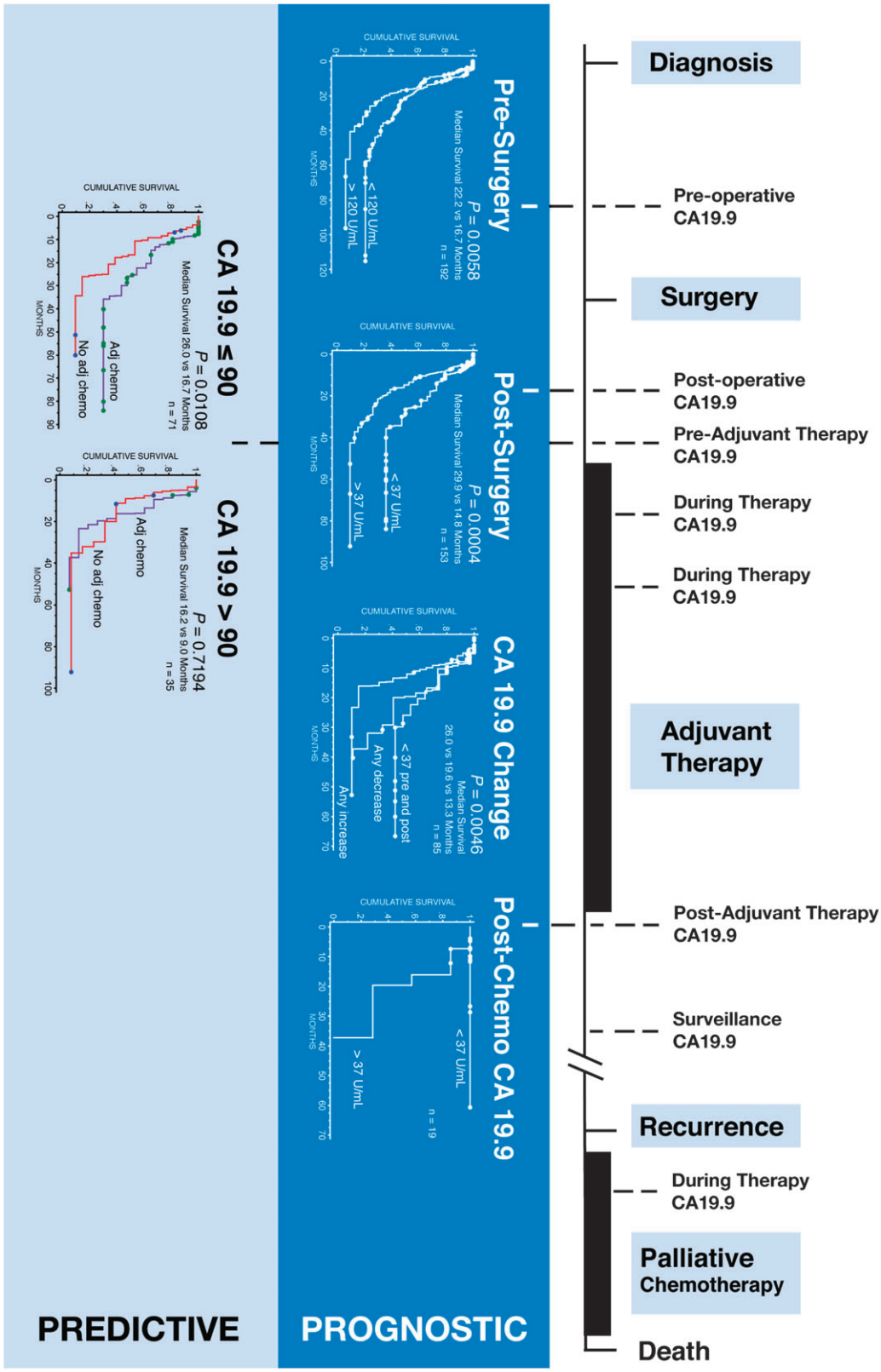

Figure 3. Schematic representation of suggested time points for CA19.9 measurements in clinical trials that would specifically address critical decision points and other applications such as surrogate end points to identify responders and non-responders early during therapy. CA19.9, carbohydrate antigen 19.9.

a normal CA19.9 after completion of adjuvant therapy is potentially associated with an excellent prognosis. These potential applications are summarized in Figure 3, which also proposes how CA19.9 levels could be incorporated in to trials to inform clinical decision making.

prognostic value of CA19.9

Postoperative CA19.9 measurements at 3 months (when hyperbilirubinamia is uncommon) co-segregate into three prognostic groups. The intermediate prognostic group of 37–120 U/ml at that time likely includes a mix of those with progressive disease and other causes of increased CA19.9 levels (biliary dysfunction and pancreatitis). This group declares itself by the 6-month stage to segregate into two prognostic groups dichotomized by the normal reference value (37 U/ml). In addition, a normal level both pre- and postoperatively identifies a group with the best prognosis, which has a 5-year survival of 42%.

The key element of the present study is that potential clinical utility was directly examined by assessing CA19.9 at specific decision-making time points. Overall, although not directly comparable, our findings with regard to the prognostic value of CA19.9 are supported by evidence from retrospective cohorts and in clinical trials. In patients undergoing pancreatic resection for PC, the preoperative CA19.9 value is associated with tumor stage, resectability, risk of recurrence and survival [13, 22–26]. Even with intercurrent biliary obstruction, which is present in ∼50% of patients, adjustment of CA19.9 levels relative to the degree of hyperbilirubinamia may still have potential prognostic value and further evaluation is encouraged. The postoperative level and the change in CA19.9 have also been correlated with survival and risk of recurrence [27–31]. Evidence is emerging that post-resection CA19.9 velocity, akin to PSA doubling time in prostate cancer, may be a better predictor of recurrence and survival [32]. In addition, for nonresectable patients, the CA19.9 at the time of diagnosis is also a prognostic factor [33].

predictive value of CA19.9

In patients undergoing systemic chemotherapy for advanced PC, the change in CA19.9 correlates with objective (radiographic) response and survival [34–37]. The poor survival of the majority of patients even with clinically localized PC who undergo resection is likely due to occult metastatic disease at the time of diagnosis. Based on the rationale of adjuvant therapy targeting low-volume disease and that serum CA19.9 is a measure of disease burden, CA19.9 may have predictive value in the adjuvant setting. A key finding in our study is that patients with a post-resection CA19.9 >90 U/ml did not achieve long-term benefit from adjuvant chemotherapy, whereas those with CA 19.9 <90 U/ml did. Previous studies have generally not addressed the relationship between CA19.9 and response to adjuvant therapy; however, assumptions were made and selection criteria altered based on CA 19.9 levels. In CONKO-001, which compared adjuvant gemcitabine to observation, patients with postoperative CA19.9 values >2.5 times the upper limit of normal (≈90 U/ml) were excluded.[4] In contrast, no CA19.9 exclusion criteria were used in ESPAC-1 and ESPACas-3 or RTOG-9704 [2, 3, 5]. In the analysis of CA19.9 data from the RTOG-9704 study of gemcitabine versus 5-FU before and after chemoradiation, Berger et al. [29] identified that patients with a CA19.9 >90 U/ml had a poor survival (23.0 versus 10.4 months). Our results suggest that patients with a post-resection CA19.9 >90 U/ml do not obtain long-term benefit from current systemic chemotherapy regimens and support integration of CA19.9 testing pre- and post-adjuvant therapy to define its role as a predictive marker and a surrogate end point.

In conclusion, assessing serum CA19.9 at specific clinically relevant time points while cognizant of its limitations has significant potential utility. These strategies should be incorporated into future clinical trials as a priority, which will define its precise role in the routine management of pancreatic cancer, and like PSA for prostate cancer, potentially become part of routine clinical practice.

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disclosure

The authors declare no conflicts of interest.

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