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REVIEW ARTICLE

Serum CA 19-9 as a Biomarker for Pancreatic Cancer—A Comprehensive Review

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Abstract Pancreatic cancer is an aggressive tumor with a dismal prognosis, biomarkers that can detect tumor in its early stages when it may be amenable to curative resection may improve prognosis. At present, serum CA 19-9 is the only validated tumor marker in widespread clinical use, but precise knowledge of its role in pancreatic cancer diagnosis, staging, determining resectability, response to chemotherapy and prognosis remains limited. A comprehensive search was performed using PubMed with keywords "pancreatic cancer" "tumor markers" "CA 19-9" "diagnosis" "screening" "prognosis" "resectability" and "recurrence". All English language articles pertaining to the role of CA 19-9 in pancreatic cancer were critically analyzed to determine its utility as a biomarker for pancreatic cancer. Serum CA 19-9 is the most extensively studied and clinically useful biomarker for pancreatic cancer. Unfortunately, CA 19-9 serum level evaluation in pancreatic cancer patients is limited by poor sensitivity, false negative results in Lewis negative phenotype (5–10%) and increased false positivity in the presence of obstructive jaundice (10–60%). Serum CA 19-9 level has no role in screening asymptomatic populations, and has a sensitivity and specificity of 79–81% and 82–90% respectively for the diagnosis of pancreatic cancer in symptomatic patients. Pre-operative CA 19-9 serum level provide useful prognostic information as patients with normal CA 19-9 serum levels (<37 U/ml) have a prolonged median survival (32–36 months) compared to patients with elevated CA 19-9 serum levels (>37 U/ml) (12–15 months). A CA 19-9 serum level of <100 U/ml implies likely resectable disease whereas levels >100 U/ml may suggest unresectablity or metastatic disease. Normalization or a decrease in post-operative CA 19-9 serum levels by ≥20–50% from baseline following surgical resection or chemotherapy is associated with prolonged survival compared to failure of CA 19-9 serum levels to normalize or an increase. Carbohydrate antigen (CA 19-9) is the most extensively studied and validated serum biomarker for the diagnosis of pancreatic cancer in symptomatic patients. The CA 19-9 serum level can provide important information with regards to prognosis, overall survival, and response to chemotherapy as well as predict post-operative recurrence. Non-specific expression in several benign and malignant diseases, false negative results in Lewis negative genotype and an increased false positive results in the presence of obstructive jaundice severely limit the universal applicability of serum CA 19-9 levels in pancreatic cancer management.

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Introduction

Pancreatic cancer is one of the leading causes of cancer related deaths worldwide. A total of 277,668 new cases and 266,029 deaths were attributed to pancreatic cancer in 2008 with an age standardized rate (annual incidence or mortality per 100,000) of 3.9 and 3.7 respectively [1]. An incidence rate nearly equal to its mortality rate demonstrates the aggressiveness and lethal nature of this disease. Population based surveys reveal that advanced pancreatic cancer is associated with a 5-year survival of 4–6% and a disease free survival of only 5% [2, 3]. This poor prognosis is attributable to late stage presentation, lack of effective treatments, early recurrence and absence of clinically useful biomarker(s) which can detect pancreatic cancer in its precursor form(s) or earliest stages [4]. At present a large number of biomarkers derived from serum, tissue, bile, pancreatic juice, saliva and/or stool have been evaluated as putative biomarkers for pancreatic cancer but most lack large scale validation [5]. Yet, despite the vast number of potential pancreatic cancer biomarkers, very few have been thoroughly evaluated and none to the extent of carbohydrate antigen 19-9 (CA 19-9). This review offers a comprehensive analysis of the utility of serum CA 19-9 as a pancreatic cancer biomarker and its use in screening, diagnosis, staging, determination of resectability, early identification of recurrence and predicting treatment response.

CA 19-9: Introduction

In 1979, Koprowoski et al. utilized hybridoma technology to identify carbohydrate antigen 19-9, a recognizable sialoganglioside first described in the colorectal cancer cell line SW1116, by using a monoclonal antibody called 1116-NS-19-9 [6]. CA 19-9 also referred to as sialyl Lewis-a (sLea), is expressed on the surface of cancer cells as a glycolipid and as an O-linked glycoprotein [7]. Subsequently, CA 19-9 was also identified in the tissue and sera of patients with other gastrointestinal tumors including esophageal, gastric, biliary and pancreatic cancer [6, 7]. CA 19-9 is derived from an aberrant pathway during production of its normal counterpart disialyl Lewis-a which has one extra sialic acid residue attached through a 2→6 linkage. Disialyl Lewis-a is normally expressed on the epithelial surface of digestive organs, serves as a ligand for monocytes and macrophages, and helps in immunosurveillance. Epigenetic silencing of the gene for 2→6 sialyl transferase during early stages of carcinogenesis leads to abnormal synthesis and accumulation of sialyl Lewis-a (CA 19-9). sLea may also play a role in cancer invasion/metastasis as it is known to be a ligand for endothelial cell E-selectin responsible for cell adhesion [8–11].

CA 19-9 is related to the Lewis blood group antigens and only patients belonging to the Le (α-β+) or Le (α + β-) blood groups will express the CA 19-9 antigen [7]. Le (α-β-) phenotypes occur in 5–10% of population which lack the enzyme 1,4-fucosyl transferase required for antigen epitope production, and as such limits the use of CA 19-9 as a universally applicable biomarker [12–15].

Carbohydrate Antigen (CA 19-9) as a Screening and Diagnostic Biomarker for Pancreatic Cancer

The utility of CA 19-9 serum levels as a screening tool for pancreatic cancer in asymptomatic individuals and in patients with symptoms suspicious for pancreatic cancer has been extensively evaluated (Table 1) [16–18]. In the largest series, Kim et al. assessed CA 19-9 serum levels among 70,940 asymptomatic individuals and identified only four patients with pancreatic cancer among 1,063 patients with CA 19-9 serum levels >37 U/ml (mean values 50.5±16.8 U/ml) [16]. These authors reported a dismal positive predictive value (PPV) of only 0.9%, although the sensitivity and specificity were 100% and 98.5% respectively. Satake et al. analyzed CA 19-9 serum levels in 12,840 asymptomatic and 8,706 individuals with symptoms suspicious for pancreatic cancer such as weight loss, epigastric pain and jaundice. The authors identified only four pancreatic cancers (one resectable) among 18 asymptomatic patients (0.2%) with an elevated CA 19-9 serum level. Among the 8,706 patients with symptoms suspicious for pancreatic cancer, 198 patients (4.3%) had elevated CA 19-9 serum levels. Following extensive work up 85 patients (1.8%) were noted to have pancreatic cancer of which 28 patients (0.4%) were resectable [16]. Similarly, Chang et al. have screened 5,343 asymptomatic individuals for pancreatic cancer, and identified CA 19-9 serum level elevation (>37 U/ml) in 385 patients (7.2%) [18]. Among this group only two patients (0.004%) had pancreatic cancer and their serum CA 19-9 levels were 88.4 U/ml and 46,885 U/ml respectively. The PPV of an elevated serum CA 19-9 level in the asymptomatic population in this study was only 0.5%. False positive elevation of the CA 19-9 serum levels was noted in 325 patients (6.1%) and a total of 58 other cancers were identified.

The above results imply that routine serum CA 19-9 level testing has no utility as a screening tool in asymptomatic patients. Even among patients with symptoms suspicious for pancreatic cancer, elevated CA 19-9 is a poor predictor of pancreatic cancer with a predictive value of 0.5–0.9%. In

Table 1 Published studies evaluating the utility of serum CA19-9 as a screening marker for Pancreatic Cancer (1980–2010)

Author, year	N=	CA 19-9 (> 37 U/ml) (N=) (%)	Pancreatic cancer (N=)	False positives (N=)	Sensitivity (%)	Specificity (%)	PPV (%)
Satake et al. 1994 [17]	12,840[a] 8,706[b]	18 (0.2%) 198 (4.3%)	4 85	14 113	NA	NA	NA
Kim et al. 2004 [16]	70,940	1,063 (1.5%)	4	1,053	100	98.5	0.9
Chang et al. 2006 [18]	5,343	385 (7.2%)	2	325	100	92.8	0.5

Published studies evaluating the role of serum CA 19-9 level suggest that it has no utility as a screening marker in asymptomatic individuals given its very low positive predictive value (0.5–0.9%). CA 19-9 serum level testing in symptomatic individuals (e.g., epigastric pain, weight loss and jaundice) is also suboptimal and identified pancreatic cancer in only 1.8% of such patients after an extensive work-up

U/ml unit/milliliter, *PPV* positive predictive value, *NA* not available

[a] Asymptomatic individuals

[b] Symptomatic individuals

7addition, in all of the aforementioned studies, a significant number of individuals with elevated CA 19-9 serum levels actually harbored non-pancreatic neoplastic pathology which significantly undermines the utility of serum CA 19-9 levels in this population. However, among patients who present with a pancreatic mass, elevated CA 19-9 serum levels yield a much higher predictive value for diagnosing pancreatic cancer. Tessler et al. studied 150 patients undergoing surgery for suspected pancreatic cancer without a preoperative tissue diagnosis. Multivariate analysis identified that a combination of weight loss >20 lbs, bilirubin >3 mg/dL, and CA 19-9 >37 U/ml provided an almost 100% specificity and positive predictive value for pancreatic cancer regardless of the extent of imaging abnormalities [19].

Two previous reviews published 20 and 7 years ago have attempted to summarize the diagnostic utility of serum CA 19-9 levels in pancreatic cancer patients [14, 20]. Steinberg analyzed the value of CA 19-9 serum levels (37–40 U/ml) in 24 case series involving 1,040 patients with symptomatic pancreatic cancer and reported a median sensitivity and specificity of 81% and 90% respectively. The positive predictive value (PPV) and negative predictive value (NPV) of an elevated serum CA 19-9 level was 72.3% and 95.8% respectively. If the serum CA 19-9 threshold used to diagnose pancreatic cancer is raised to 100 U/ml or 1,000 U/ml, the specificity increased to 98% and 99.8%, moreover the sensitivity decreased to 68% and 41% respectively [20]. More recently, Goonetilleke et al. analyzed the utility of CA 19-9 serum levels (37–40 U/ml) to diagnose pancreatic cancer among 2,283 symptomatic patients reported in 26 case-series. [14] In this report, the sensitivity and specificity of an elevated serum CA 19-9 level was 79% and 82% with a PPV and NPV of 72% and 81% respectively. Overall, an elevated serum CA 19-9 level has a sensitivity of 79–81% and a specificity of 82–90% for diagnosing pancreatic cancer in symptomatic patients.

CA 19-9 Serum Levels as a Biomarker for Assessing Clinical Stage and Determining Surgical Resectability in Patients with Pancreatic Cancer

The usefulness of pre-operative serum CA 19-9 levels to predict pancreatic cancer stage and determine resectability has been extensively studied [21–26] (Table 2). Kim et al. evaluated CA 19-9 serum levels in 114 pancreatic cancer patients who underwent either pancreatic resection (*N*=72) or palliative bypass surgery (*N*=42). These authors reported a positive correlation between pancreatic cancer stage and mean pre-operative CA 19-9 serum levels. In this study stage IA patients had a mean serum CA 19-9 level of 40.05 U/ml, stage IIA patients had mean serum levels of 469.64 U/ml, stage IIB patients had mean serum levels of 747.79 U/ml, stage III patients had mean serum levels of 709 U/ml, while stage IV patients had a mean serum CA 19-9 levels of 3,239 U/ml [25]. Safi et al. compiled preoperative CA 19-9 serum levels in 126 patients with resectable pancreatic cancer [22]. In this study, 29 of 45 patients (64%) with stage-I pancreatic cancer had elevated CA 19-9 with a median level of 68 U/ml (range, 9.0–3,018 U/ml). Eight of ten patients (80%) with stage-II pancreatic cancer had elevated serum CA 19-9 level with a median levels of 72 U/ml (range, 8.4–5,000 U/ml). Eighty one percent (47 out of 58) of patients with stage III disease had an elevated CA 19-9 levels (median, 210 U/ml, range, 2–7,496 U/ml) and 100% of patients (*N*= 13) with stage-IV disease had an elevated CA 19-9 serum levels (median 412 U/ml, range, 49.6–14,600 U/ml). In an effort to correlate advanced stage disease with higher CA 19-9 serum levels, these authors also noted that an elevated pretreatment CA 19-9 serum level of ≥300 U/ml indicated unresectable disease in 80% of patients. That said, it is important to remember that 5–10% of patients with pancreatic cancer will not demonstrate elevated serum CA 19-9 serum levels given their sialyl Lewis negative state and as such

Table 2 Published studies analyzing the correlation between CA 19-9 serum levels and Pancreatic Cancer stage (1980–2010)

Author, year	N=	Stage (AJCC)	CA 19-9 level (U/ml)	
			Mean	Median
Pleskow et al. 1989 [21]	6	I–III	1,522	151
	14	IV	20,720	343
Safi et al.1997 [22]			Median (range) (U/ml)	
	29	I	68 (9.0–3,018)	
	8	II	72 (8.4–5,000)	
	47	III	210 (2–7.496)	
	13	IV	412 (49.6–14,600)	
Jiang et al. (2004) [23]			Median±SD (U/ml)	
	2	I	26.31±6.56	
	5	II	875.45±329.31	
	25	III	1,223±479.73	
	97	IV	2018.19±731.36	
Ferrone et al. (2006) [24]			Median (U/ml)	
	14	IA	20.5	
	18	IB	86	
	42	IIA	105	
	97	IIB	164	
	5	IV	182	
Kim et al. (2009) [25]			Mean (U/ml)	Median±SD (U/ml)
	4	IA	40.05	40.05±23.85
	32	IIA	469.64	469.64±1,055.86
	23	IIB	747.79	747.79±2,044.71
	20	III	709.98	709.98±1,392.65
	33	IV	3,239	3,239.06±4,074.25
Kondo et al. (2010) [26]	11	I	96	
	98	II–IV	160	

Published studies demonstrate a strong correlation between elevated preoperative CA 19-9 serum levels and subsequent pancreatic cancer clinical stage. Eighty to 90% of patients with advanced pancreatic cancer (stage III-IV) will have a markedly elevated CA 19-9 serum level of >100 U/ml

AJCC American Joint Commission on Cancer, *U/ml* unit/milliliter, *SD* standard deviation

this correlation is not universal [7]. Moreover, CA 19-9 serum levels alone should not be the sole criteria used in making decisions to proceed to surgery; rather CA 19-9 serum levels is one of several contributing factors used in combination with clinical evaluation and information obtained from radiological and endoscoping imaging.

Advances in radiologic [CT scan, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET scan) and endoscopic imaging (Endoscopic Ultrasound (EUS), ERCP)] as well as the use of laparoscopy have enabled better delineation and staging of pancreatic cancer and helped to reduce the negative laparotomy rate [27, 28]. Nevertheless, up to 15% of patients with pancreatic cancer are found unresectable at the time of surgery, which is attributable to occult vascular invasion, presence of undetected metastasis or positive peritoneal lavage cytology [25]. Whether pre-operative CA 19-9 serum levels can serve as a surrogate marker for tumor resectability has been extensively evaluated [22, 25, 26, 29–36] (Table 3). Schleiman et al. evaluated preoperative CA 19-9 serum levels in 89 pancreatic cancer patients prior to surgical exploration and noted that mean CA 19-9 serum levels were significantly lower in resectable tumors compared to those with locally advanced tumors (63 vs. 592 U/ml, $p<0.003$) or with metastatic disease (63 vs. 1,387 U/ml, $p<0.001$) [32] (Table 3). A pre-operative CA19-9 serum level of >150 U/ml was associated with an 88% positive predictive value for unresectability, whereas serum levels <150 U/ml had a negative predictive value of 64% [32]. Kim et al. evaluated CA 19-9 serum levels in 72 patients treated surgically for "resectable" pancreatic adenocarcinoma and 42 patients treated with surgical palliation (bypass surgery). The median CA 19-9 serum levels for patients achieving an R0 resection, R1 resection or R2 resection, was 49.66, 233.0 and 600 U/ml respectively. The median CA 19-9 serum level for patients with peritoneal metastasis was 780.49 U/ml. These authors concluded that a pre-operative CA 19-9 ≥92.77 U/ml predicted an R1/2 resection or unresectability with a 90.6% accuracy. It is important to note however that lower pre-operative CA 19-9 serum levels predicted the probability of an R0 resection in only 27.1% of patients [25]. In summary, these studies suggest that a median CA 19-9 serum level <100 U/ml correlates with resectability (41–80%) whereas levels >100 U/ml suggest advanced or metastatic pancreatic cancer (60–85%) (Table 3).

Table 3 Published studies analyzing the correlation between serum CA 19-9 level and Pancreatic Cancer resectability (1980–2010)

Author, Year	N=	Tumor status	CA19-9 serum levels (U/ml)	
			Median	Mean
Paganuzzi et al. 1988 [29]	7	Resectable	NA	94±59
	19	Unresectable		563±768 ($p>0.05$)
Safi et al. 1997 [22]	106	Resectable	152	NA
	199	Unresectable	512	
Nakao et al. 1998 [30]	18	Resectable	NA	<1,344
	130	Unresectable		>2,000 (range 5–32,240)
Kau et al. 1998 [31]	19	Resectable	NA	524±70 ($p<0.002$)
	40	Unresectable		3,114±1,643
Schleiman et al. 2003 [32]				Mean±SD (U/ml)
	40	Resectable	73.5	386±1,169
	49	Unresectable	374	1,568±2,979 ($p<0.001$)
	25	Locally advanced	336	1,090±1,541 ($p<0.003$)
	24	Metastatic	431	2,066±3,942 ($p<0.01$)
Kilic et al. 2004 [33]	18	Resectable	19.3	111.98±156.23 ($p<0.034$)
	15	Unresectable	302	1,860.14±3,091.43
	18	Disseminated	500	3,188.09±4,089.71 ($p<0.004$)
	9	Peritoneal Metastasis	780.49	3,967.94±4,703.70 ($p<0.113$)
Fujioka et al. 2007 [34]			Median	
	93	R0 Resection	78	
	66	R1/2 Resection	155	
	85	Locally advanced/Metastatic	326	
Maithel et al. 2008 [35]	211	Resectable	131	
	51	Unresectable	379	
Zhang et al. 2008 [36]			Median	Predictive value
	54	Resectable	<353	84.38% (+)
	36	Unresectable	>352	90.00% (−)
Kim et al. 2009 [25]			Median	Mean±SD
	24	R0 Resection	49.66	111±156.23 ($p<0.0034$)
	48	R1/2 Resection	233.03	1,860±3,091
	42	Unresectable	174.07	1,560±2,985
Kondo et al. 2010 [26]			Median	
	77	R0 Resection	118	
	11	R1/2 Resection	203	

Published studies suggest that pre-operative CA 19-9 serum levels are highly correlated to subsequent pancreatic cancer resectability rates. A median CA 19-9 serum level of <100 U/ml correlates with resectability (positive predictive value, PPV of 60–80%) whereas CA19-9 levels higher than >100 U/ml suggested advanced or metastatic disease with a PPV for unresectability of 88–91%.

U/ml unit/milliliter, *SD* standard deviation, *NA* not available, *R0* resection-microscopic margin tumor free, *R1* resection-microscopic margins positive for tumor, *R2* resection- macroscopic tumor left behind

CA 19-9 Serum Levels as a Biomarker of Prognosis in Patients with Pancreatic Cancer

The utility of serum CA 19-9 levels to provide meaningful prognostic information and permit patient stratification (survival groups) based on CA 19-9 serum level has been extensively evaluated [22, 24, 26, 30, 31, 36–49] (Table 4). Waraya et al. performed a multivariate analysis of factors predicting survival in 117 pancreatic cancer patients undergoing surgical resection and reported that a low preoperative CA 19-9 serum levels (28-30 U/ml) ($p<0.0016$, relative risk (RR), 2.16) and positive peripancreatic margin ($p<0.04$, RR, 1.62) independently predicted survival [46]. Moreover they noted that the higher the preoperative CA19-9 level, the worse the prognosis. Patients with a preoperative CA 19-9 serum levels of <37 U/ml [$N=23$] had a 5-year disease

Table 4 Published studies analyzing a correlation between pre-operative CA 19-9 serum levels and Pancreatic Cancer prognosis (1980–2010)

Author, Year	N=	CA 19-9 cut-off levels (U/ml)	Median survival (months)
Sperti 1993 [38]	15	<1,096	22 ($p<0.001$)
	15	>1,096	8
Lundin 1994 [39]	69	<370	9.5 ($p<0.001$)
	82	>370	4.4
Safi et al. 1997 [22]	89	<400	17.3 ($p<0.0001$)
	37	>400	7.1
Nakao et al. 1998 [30]	64	<2,000	60
	15	>2,000	19
Kau et al. 1999 [31]	7	<35	36 ($p<0.028$)
	46	>35	12
Ikeda 2001 [40]	17	<1,000	10.3 ($p<0.001$)
	38	>1,000	7.2
Saad et al. 2002 [41]	28	<1,212	14.9 ($p<0.001$)
		>1,212	7.4
Micke et al. 2003 [42]	95	<420	12.3 ($p<0.01$)
		>420	7.0
Berger et al. 2004 [43]	7	Undetectable	32
	21	≤37	35
	44	38–200	22
	57	200	16
Maisey et al. 2005 [44]	154	<958	11.2 ($p<0.0004$)
		>958	7.5
Ferrone et al. 2006 [24]			Median survival (years)
	66	<37	2.4 ($p<0.01$)
	45	>37	1.6
	90	<200	2.3 ($p<0.001$)
	21	>200	0.9
Smith et al. 2008 [45]			Median survival (months)
	64	<150	22.1
	45	>150	10.4 ($p<0.02$)
Waraya et al. 2009 [46]			5-Year DSS (months)
	23	<37	30.6 ($p<0.0001$)
	66	>37	12.7
Turrini et al. 2009 [47]	50	<37	22 ($p<0.02$)
	27	400–900	15
	26	>900	12
Wasan et al. 2009 [48]	95	<1,096	12.2 ($p<0.0001$)
		>1,096	5.0
Kondo et al. 2010 [26]			3-Year survival (%)
	32	<37	57
	37	>37	30
	81	<500	42
	28	>500	13
Katz et al. (2010) [49]			Median survival (months)
	21	<37	52.8
	78	>37	21.2 ($p<0.02$)

Pre-operative CA 19-9 serum levels in pancreatic cancer patients correlate not only with stage of disease, but also independently predict overall survival. An undetectable level or a CA 19-9 serum level of <37 U/ml is associated with a median survival of 22–40 months compared to a median survival of 7–30 months in patients with a pre-operative CA 19-9 serum level of >37 U/ml

DSS disease specific survival, *U/ml* unit/milliliter

specific survival (DSS) of 60.0% compared to 4.0% DSS among patients with CA 19-9 serum levels >37 U/ml [N=66] (P<0.0001). Even more notable was the fact that 76.9% of stage III pancreatic cancer patients with a CA19-9 serum level of <37 U/ml survived more than 5 years (average DSS of 26.9 months). Barugola et al. analyzed factors predictive of early death (within 12 months) among 224 surgically resected pancreatic cancer patients and reported that an elevated preoperative CA 19-9 serum levels of >200 U/ml, a high grade tumor, an R2 resection and prolonged symptoms independently predicted early death (within 12 months) [46]. Berger et al. stratified 129 surgically resected pancreatic cancer patients into four 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 38–200 U/ml or >200 U/ml (22 and 16 months, respectively) [43]. 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) [45]. Table 3 lists additional studies which have used various cut-off levels for pre-operative CA 19-9 serum levels in an effort to predict survival among pancreatic cancer patients [22, 24, 26, 30, 31, 36–49]. These studies support the conclusion that a normal (<37 U/ml) or low preoperative CA 19-9 serum level (<100 U/ml) correlates with early pancreatic cancer stage and independently predicts improved overall survival, whereas an elevated CA 19-9 serum levels (>100 U/ml) is associated with a poor prognosis.

Several authors have reported on the prognostic significance of the post-operative CA 19-9 serum levels in predicting survival. Ferrone et al. analyzed 111 pancreatic cancer patients in whom pre- and post-operative CA 19-9 serum levels were measured. Post-operative CA 19-9 serum levels of <37 U/ml were associated with a mean survival of 2.4 years, a level of <200 U/ml had a mean survival of 2.3 years, whereas a post-operative CA 19-9 serum levels of <1,000 U/ml and >2,000 U/ml had a mean survival of 9 and 5 months respectively. Overall a low postoperative serum CA 19-9 level (<200 U/ml) was an independent predictor of survival [36, 37].

Kondo et al. studied pre- and postoperative CA19-9 serum levels in 109 surgically treated pancreatic cancer patients and identified that both a normal postoperative CA 19-9 serum level (37 U/ml) (Hazard Ratio (HR) 1.64, p<0.004), and the addition of adjuvant chemotherapy were an independent predictors of prognosis [26]. More specifically these authors identified that a post-operative CA 19-9 serum level measured at 2–5 weeks could independently predict a prolonged 3-year survival rate (%). Post-operative CA 19-9 serum levels of <37 U/ml, <200 U/ml and >500 U/ml were associated with a 49%, 38%, and 0% 3-year survival rates respectively. Elevated CA 19-9 (>35 U/ml) in the immediate post-operative period was also associated with an R1 resection and lymph node metastases (p<0.041) [26]. Montgomery et al. assessed 40 pancreatic cancer patients who had undergone surgical resection and found that patients in whom the CA 19-9 serum levels returned to normal within the first postoperative year had a longer overall survival compared to patients in whom CA 19-9 serum levels remained elevated (34 vs.13 months, p<0.04) [50–52]. Given the half life of CA 19-9 is approximately 14 h, those authors suggested that post-operative CA 19-9 serum levels should be measured 4–6 weeks following surgery and that patients with elevated levels are likely to harbor residual tumor or sub-clinical metastases. In summary, postoperative normalization or a downward trend of the CA 19-9 serum level following pancreatic resection is associated with prolonged survival whereas elevated or failure of the CA 19-9 to decrease following pancreatic resection reflects residual disease or occult metastasis and portends a poor survival.

CA 19-9 Serum Levels as a Biomarker for Chemotherapy Response in Pancreatic Cancer Patients

Whether serum CA 19-9 levels can be used as a surrogate marker of response to chemotherapy has been studied in a variety of clinical settings [41, 44, 53–64]. Willett et al. measured CA 19-9 serum levels in 42 resectable pancreatic cancer patients receiving neoadjuvant treatment with 5-flourouracil and external beam radiation prior to planned pancreaticoduodenectomy. Among ten patients with an increased CA 19-9 serum level following treatment, 9 (90%) had distant metastases or local tumor progression. In contrast, only six of 29 patients (21%) with a declining CA 19-9 serum level after neo-adjuvant chemo-radiotherapy had metastases or local tumor progression on restaging CT scan or at laparotomy. Whether the CA 19-9 serum level increased or decreased during treatment, correlated significantly with disease progression (p<0.009) [65]. Katz et al. studied 119 patients with pancreatic cancer who were treated with neoadjuvant chemotherapy followed by pancreaticoduodenectomy. These authors found that a post-treatment CA 19-9 serum level of <37 U/ml had an 86% PPV for successful completion of the pancreatic resection, and a NPV of only 33%. Post-treatment CA 19-9 serum levels <61 U/ml also had a high PPV of 93% but a diminishing NPV of 28% in regards to predicting successful completion of pancreati-

coduodenectomy among resectable patients [49]. Although post-treatment CA 19-9 serum levels in the above mentioned study had a high PPV in regards to likelihood of resectability following neo-adjuvant chemotherapy, the low NPV highlights the importance of re-staging radiographic evaluation as well as laparoscopy prior to surgical exploration [34, 49].

Several authors have reported on the use of CA 19-9 serum level trends to assess chemotherapy response using such definitions as ≥20% or ≥50–75% decline in CA 19-9 serum levels within the first 6–8 weeks of treatment. Nearly all studies have demonstrated that a treatment related decline in CA 19-9 serum levels is associated with prolonged survival and is an independent predictor of overall survival [41, 44, 53–64] (Table 5). Reni et al. compared basal CA 19-9 serum levels in 247 advanced pancreatic cancer patients enrolled in five consecutive chemotherapy trials (G, gemcitabine; PEFG, cisplatin, epirubicin, 5-fluorouracil, and gemcitabine; PDXG, cisplatin, docetaxel, capecitabine, and gemcitabine) [60]. The survival curves were plotted based on a pre-defined decline in CA 19-9 serum levels (Group 1, <50% decrease, Group 2, 50% to 89% decrease and Group 3, >89% decrease). Patients with a higher percent decline in CA 19-9 serum levels following treatment had improved overall survival (Group III-16.7 months compared to Group II-10 months, $p<0.002$, and Group II- 10 months vs. 6.5 months for Group -I, $p<0.002$). Overall, the median survival was 15.5 months among patients with normal CA 19-9 levels, 11.9 months among 108 patients with CA 19-9 serum levels between 38 U/ml and 1,167 U/ml and 8 months among 105 patients who had CA 19-9 serum levels >1,167 U/ml [60].

Halm et al. evaluated CA 19-9 serum levels in 36 patients enrolled in gemcitabine chemotherapy trials and reported that patients with a decline in CA 19-9 serum levels of >20% from baseline after 8 weeks of treatment ($N=25$) had improved median survival compared to patients with a rise or a decrease of <20% ($N=11$) (268 vs. 110 days, $p<0.001$) [55]. Moreover, treatment related decline in CA 19-9 serum levels was the strongest independent predictor of survival ($p<0.001$) on multivariate analysis. Finally, using a novel approach to compute log CA 19-9 kinetics among 115 patients enrolled in first line pancreatic cancer chemotherapy, Boeck et al. demonstrated that log CA 19-9 kinetics was a significant predictor of both time to tumor progression (Hazard Ratio, HR 1.48, $p<0.001$) and overall survival (HR 1.34, $p<0.001$) [66].

CA 19-9 Serum Levels as a Biomarker to Predict Post-operative Recurrence

The utility of sequential post-operative CA 19-9 serum level measurement to detect early recurrence in pancreatic cancer patients has been well studied. Kang et al. evaluated factors predictive of post-operative recurrence in 61 pancreatic cancer patients and reported that an adjusted CA 19-9 serum level (defined as a ratio of CA 19-9 serum levels divided by serum bilirubin when higher than 2 mg/dl) of >50 U/ml was associated with an increased recurrence risk (twice) when compared to adjusted levels of <50 U/ml [67]. Montgomery et al. reported that a significant and sustained post-operative elevations of CA 19-9 serum levels preceded clinical or radiologic detection of recurrence by 2 weeks to 5 months (median 3.5 months) and that an elevated post-operative CA 19-9 serum levels >180 U/ml was associated with a disease free survival of 12 months compared to 35 months for patients with post-operative CA 19-9 serum levels <180 U/ml [50]. In this study, patients whose postoperative CA 19-9 values normalized by 3 to 6 months (<37 U/ml) had a longer disease free survival (24 vs. 10 months, $p<0.04$) and median survival (34 vs. 13 months, $p<0.04$). Hernandez et al. analyzed data from 96 surgically resected pancreatic cancer patients in whom CA 19-9 serum levels were drawn at baseline, 4 weeks, and 12-week intervals following surgery and for whom CA 19-9 velocity was calculated (rate of change in CA 19-9 levels over a 4-week period). These authors found that CA 19-9 velocity was a better predictor of overall survival than baseline CA 19-9 serum levels ($p<0.001$). Patients with disease progression had a CA 19-9 velocity of 131 U/ml/4-weeks compared to a velocity of 1 U/ml/4-weeks at 22 months for patients without disease progression ($p<0.001$) [51]. In summary, the above results imply that clinical or radiologic post-operative recurrence is often preceded or associated with elevated CA 19-9 serum levels by 2–6 months. Elevation of post-operative CA 19-9 serum levels or failure of the CA 19-9 serum levels to normalize in the post-operative period suggest the presence of residual tumor or remnant disease and is associated with a poor prognosis.

Limitations of CA 19-9 Serum Levels as a Pancreatic Cancer Biomarker

Despite multiple clinical applications for CA 19-9 serum levels in pancreatic cancer patients, the diagnostic utility of CA 19-9 is often limited due to a low or modest sensitivity (79–81%) in symptomatic patients [12, 14, 15]. Moreover, a very low PPV (0.9%) makes CA 19-9 serum levels a suboptimal test to screen asymptomatic populations [16–18]. Even among individuals at higher risk of pancreatic cancer (hereditary pancreatitis, family history of pancreatic cancer, Peutz-Jeghers syndrome), CA 19-9 serum levels fail to identify early/small tumors or precancerous lesions in 10–15% of patients [68] and is elevated in only 80–85% of

Table 5 Published studies analyzing the utility of CA 19-9 serum levels for monitoring treatment response following adjuvant and palliative chemotherapy for pancreatic cancer (1980–2010)

Author, year	N=	% change in CA19-9 serum level after treatment (%)	Median survival (months)	p value
Ishii et al. 1997 [53]	66	>50%	4.7	NA
		<50%	2.9	
Gogas et al. 1998 [54]	35	≥15%	11.1	<0.001
		≤15%	6.2	
Halm et al. 2000 [55]	43	>20%	8.9	<0.001
		<20%	3.7	
Saad et al. 2002 [41]	28	≥50%	13.8	<0.002
		≤50%	9.8	
Stemmler 2003 [56]	87	>50%	9.8	<0.022
		<50%	5.8	
Ziske et al. 2003 [57]	46	>20%	12.8	<0.006
		<20%	8.1	
Ko et al. 2005 [58]	76	>25%	9.61	<0.001
		<25%	4.64	
		>50%	10.8	<0.001
		<50%	5.82	
		>75%	12.0	<0.001
		<75%	6.0	
Pohlank et al. 2008 [59]	181	>20%	12.5	<0.003
		<20%	8.7	
Reni et al. 2009 [60]	67	<50%	6.5	<0.001
	75	50–89%	10	
	62	>89%	16.7	
Maisey et al. 2005 [44]			Hazard ratio, 95% CI	
	88	<20%	1.95, 1.11–3.42	
		>20%		<0.019
Hess et al. 2008 [61]	175	≥50%	1.11, 0.81–1.52	<0.53
		≤50%		
Fogelman et al. 2008 [62]	143	>50%	0.46, 0.25–0.85	<0.01
Haas et al. 2010 [63]	70	>20%	2.00	<0.018
Takahashi et al. 2010 [64]	31	SD*	reference	<0.0001
	27	MD+	2.85, 2.49–3.18	
	6	Increased	16.9, 4.81–58.8	

CA 19-9 serum levels are a reliable marker of chemotherapy response. A CA 19-9 serum levels which decreases to ≤20–50% of baseline levels within the first 6–8 weeks of treatment predicts prolonged survival and is an independent predictor of overall survival

NA not available, *CI* confidence interval, *SD** substantially decreased = pre-chemotherapy CA 19-9 (pre-CA 19-9) of <370 U/ml and Pre chemotherapy CA 19-9 serum level/Post chemotherapy CA 19-9 serum level ratio of <10%, *MD*+ moderately decreased = pre-chemotherapy CA19-9 of <370 U/mL and Pre-chemotherapy CA 19-9 serum level/Post chemotherapy CA 19-9 serum level ratio of 10-50%; Increased = pre-chemotherapy CA 19-9 serum level/post-chemotherapy CA 19-9 serum level ratio of >100%

pancreatic cancer patients [12, 14, 20]. As noted earlier, CA 19-9 serum levels may be elevated in a variety of non-pancreatic neoplastic conditions resulting in a high false positive rate (10–30%). Benign conditions associated with elevated serum CA 19-9 levels include ovarian cyst, heart failure, hashimoto's thyroiditis, rheumatoid arthritis and diverticulitis [16–19, 69–74] (Table 6). Marked elevations in CA 19-9 serum levels have also been reported in numerous benign and malignant biliary conditions (15–38.8%) such as choledocholithiasis, gall bladder cancer and cholangiocarcinoma. Finally, CA 19-9 serum levels alone cannot differentiate between benign, precursor lesions and malignant pancreatic conditions such as acute and chronic pancreatitis, intraductal pancreatic mucinous neoplasm (IPMN), pancreatic intra-epithelial neoplasia (PANIN) and pancreatic cancer as the former are also associated with elevated CA 19-9 serum levels in 10–50% of cases [69–75].

Hyperbilirubinemia is also a significant confounding factor since it is associated with an increased CA 19-9 serum level in cases of both benign and malignant biliary obstruction [8, 9, 12, 20]. Although CA 19-9 serum levels in the presence of obstructive jaundice may have higher sensitivity, it is at the cost of decreased specificity and accuracy. Mery et al. studied 548 patients with obstructive

Table 6 Benign and malignant conditions associated with false positive elevations of CA 19-9 serum levels

Organ/system	Pathologic condition	CA 19-9 range (U/ml)
Pancreatic diseases [16, 69, 70]	Acute pancreatitis Chronic pancreatitis	3–22
	Pancreatic abscess Pseudo-pancreatic cyst	
Hepato-biliary diseases [13, 16, 71, 72]	Cholangio-carcinoma Cholangitis	50–99,00
	Choledocholithiasis	
	Cholelithiasis	
	Cirrhosis of liver Hepatitis	
	Hepatocellular carcinoma	
	Liver cyst	
	Liver abscess	
	Polycystic liver disease	
GI malignancies [15–20]	Colorectal cancer Esophageal cancer Gastric cancer	37–100
Miscellaneous [15–20, 73, 74]	Bronchitis Congestive heart failure	112–1,338
	Cystic fibrosis	
	Diverticulitis	
	Hashimoto's thyroiditis Lung cancer	
	Ovarian cyst	
	Pleural effusion	
	Renal cyst	
	Rheumatoid arthritis	

False positive elevations of the CA 19-9 serum level have been noted in a variety of pathological conditions, most notably in the presence of obstructive jaundice. As such, CA 19-9 serum levels cannot be used to differentiate benign from malignant pancreatic diseases

U/ml unit/milliliter, *GI* gastrointestinal

jaundice and reported a higher CA 19-9 serum level among pancreatic cancer patients compared to those with other hepatobiliary malignancies or benign diseases. These authors noted that by increasing the cut-off level for CA 19-9 serum level from 37 to 90 U/ml they were better able to differentiate malignant hepatobiliary diseases from benign diseases (sensitivity 86% vs. 61% and specificity 39% vs. 86%) [75]. Kau et al. studied 86 resectable and 57 unresectable pancreatic cancer patients and reported that a mean CA 19-9 serum levels of 191±6 U/ml and 1,203± 400 U/ml was associated with serum bilirubin levels of <7.3 mg/dl or >7.3 mg/dl respectively [31]. Ong et al. studied 83 patients presenting with abnormal CA19-9 serum levels and radiological or clinical features suggestive of hepato-biliary-pancreatic (HPB) malignancy who were subsequently found to have benign disease. On multivariate analysis, these authors reported that hyperbilirubinemia (serum bilirubin >2 mg/dl) was an independent factor predictive of CA 19-9 serum level ($p<0.028$) [76, 77].

Biliary drainage which results in a decrease in CA 19-9 serum levels suggests benign conditions. Marrelli et al. studied 128 patients admitted with obstructive jaundice including 87 patients with pancreatico-biliary malignancy and 42 patients with benign diseases. CA 19-9 serum levels were elevated in 61% of benign causes and 86% of malignant causes, which resulted in a reduction in accuracy to 61%. Following biliary drainage CA 19-9 serum levels decreased in nearly all benign cases (41 of 42 patients, 98%) but in only 19 out of 38 (50%) patients with malignant biliary obstruction [78]. Kau et al. reported a 40% reduction in CA 19-9 serum levels after relief of malignant biliary obstruction. Several authors have postulated that inflammation associated with obstructive jaundice increases proliferation of biliary epithelial cells with a subsequent increase in systemic absorption of CA 19-9. The CA 19-9 serum levels normalize after treatment of benign cholestasis, whereas it remains elevated in malignant obstruction due to persistent production of CA 19-9 by proliferating tumor cells [31].

In an effort to increase the specificity and accuracy of CA 19-9 serum evaluation in the setting of hyperbilirubinemia, several authors have suggested using higher cut-off levels for serum CA 19-9 or choosing a level determined by receptor operator characteristic (ROC) curves associated with higher specificity. Marrelli et al. evaluated an increased serum CA 19-9 cut-off level of 90 U/ml, and noted that the specificity increased to 95%, while the sensitivity declined to 61% [78]. Similarly, using a CA 19-9 serum cut-off level of >1,000 U/ml in the presence of hyperbilirubinemia, Kim et al. reported a specificity of nearly 100%, but a sensitivity of less than 50% [25]. Ortiz-Gonzalez et al. studied 26 patients with resectable pancreatic cancer and found that the median adjusted CA

19-9 serum level was significantly lower ($p<0.01$) among patients with normal biliary excretion than those with bilirubin levels >2 mg/dL [79]. Kang et al. assessed the value of adjusted CA 19-9 serum levels to predict post-operative recurrence in 61 patients who underwent pancreatic resection. Adjusted preoperative CA 19-9 serum levels were significantly lower compared to baseline CA 19-9 serum levels (129.4±225.2 U/ml vs. 442.1±645.5 U/ml, $p<0.0001$). In this study an adjusted preoperative CA 19-9 serum level of ≥50 U/ml ($p<0.027$) was an independent predictive factor for tumor recurrence [67].

Finally, as mentioned earlier, sialyl Lewis negative phenotype seen in 5–10% of population is associated with false negative results for CA 19-9 serum levels even in the presence of advanced pancreatic cancer [7]. Other biomarkers such as duke pancreatic monoclonal antigen type 2 (DUPAN-2), macrophage inhibitory cytokine (MIC-1), regenerating islet derived (REG-4) which are unaffected by Lewis blood group status may be more effective for this population. [7, 80–82] Additional strategies include simultaneous measurement of disialyl Lewis a (normal counterpart) during CA 19-9 evaluation. The ratio of sLea (CA 19-9)/disialyl Lewis may provide an improved serum diagnosis by averting undesired effect of a Lewis-blood group negative phenotype and reducing the false-positive rate (non-specific elevation) [7].

Conclusion

Pancreatic cancer is associated with a dismal prognosis and biomarkers that can detect pancreatic cancer in its earliest stages should improve prognosis. Despite a large number of putative biomarkers for pancreatic cancer, carbohydrate antigen (CA 19-9) is the most extensively studied and currently the gold-standard biomarker for pancreatic cancer diagnosis in symptomatic patients. Pre-operative CA 19-9 serum levels provide important prognostic information in pancreatic cancer patients, correlate with tumor stage and independently predict overall survival. An increasing postoperative CA 19-9 serum level or failure of the CA 19-9 serum levels to normalize post-operatively is associated with a poor prognosis and suggests residual disease or the presence of occult metastases, while a decline or normalization of the post-operative CA 19-9 serum level, is associated with improved survival. CA 19-9 serum levels assessment can be used as a surrogate marker of response to chemotherapy with a ≥20–50% decrease in CA 19-9 serum levels following chemotherapy associated with a positive tumor response and increased survival. Limitations such as false negative results in sialyl Lewis negative individuals and false positive elevation in the presence of obstructive jaundice limit the universal applicability of serum CA 19-9 and the poor PPV of CA 19-9 serum level makes it impotent as a screening tool.

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