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CA 19-9 Stratification in Pancreaticobiliary Malignancies: Low Levels Predict Superior Survival Independent of Metastases and Curative Therapy

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ABSTRACT

CA 19-9 remains the most frequently applied serum indicator in the clinical workup of pancreaticobiliary malignancies (PBMs), yet there is minimal published information describing how patients with PBMs behave when their CA 19-9 levels are undetectable or only minimally elevated (referred to here as "low"). This project aimed to determine how individuals with PBMs and low CA 19-9 values compare—both in presentation and in clinical trajectory—to those whose CA 19-9 concentrations at diagnosis were normal or elevated. We performed a retrospective review of biopsy-verified PBM cases and assigned each individual to one of three diagnostic CA 19-9 categories. Survival probabilities for these groups were produced with the Kaplan–Meier approach, and comparisons were analyzed with Cox proportional hazards regression. Among 283 total patients, 23 (8.1%) fell into the low CA 19-9 group, 70 (24.7%) into the normal range, and 190 (67.1%) into the elevated range. When adjusting for age, sex, body mass index, metastatic disease at presentation, and whether curative-intent therapy was provided, the elevated CA 19-9 cohort demonstrated a hazard ratio for death of 1.993 (95% CI 1.089–3.648; p = 0.025) when contrasted with the low-level group. Elevated CA 19-9 (versus low levels) and the existence of metastases both increased mortality risk, while receiving curative-intent treatment lowered that risk.

Keyword: Cancer detection, Tumor indicators, Adenocarcinoma, Pancreatic cancer

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Introduction

Pancreaticobiliary cancers continue to represent a major global health burden, accounting for 550,698 new diagnoses and 611,722 deaths worldwide in 2020 [1]. In 2021, the United States alone reported 72,410 new diagnoses and 52,530 related deaths [2]. Despite therapeutic advances, SEER data still place the 5-year relative survival rate near 10% [3]. Their dismal prognosis reflects late-stage discovery, limited effective therapy in advanced disease, and the inherently aggressive biology of these tumors [4, 5].

CA 19-9, a serum carbohydrate antigen, is routinely incorporated into management strategies for PBMs—such as pancreatic ductal adenocarcinoma (PDAC), cholangiocarcinoma (CCA), and gallbladder carcinoma (GBCA). Reported sensitivity rests at 79–81% and specificity at 82–90%, although its positive predictive value of 72.3% severely limits screening potential [6]. CA 19-9 lacks disease-specificity: elevations occur in unrelated cancers (e.g., mucinous ovarian tumors, endometrial malignancies, lung cancer) [7–9] and various benign disorders, including biliary obstruction, pancreatitis, and renal dysfunction [10–15]. Its utility is also undermined by genetics: CA 19-9 is a monosialylated Lewis A antigen, meaning people who are Lewis antigen–negative produce minimal or no CA 19-9 [16]. Of the major Lewis phenotypes—Le(a−b−), Le(a+b−), and Le(a−b+)—only the Le(a−b−) group cannot synthesize the antigen; roughly 5–10% of Caucasians fall into this category [6, 10], which can falsely imply "low" CA 19-9 even in the presence of PBMs.

Although high CA 19-9 concentrations generally correlate with poorer outcomes in PDAC and declines following treatment typically reflect improved prognosis [17–25], very few studies have specifically focused on patients

whose CA 19-9 levels are low or unmeasurable. Given the high mortality associated with PBMs, clarifying the role of CA 19-9 in this subgroup may refine prognostic evaluation and management strategies.

This investigation analyzed clinical profiles and outcomes for patients within the Los Angeles County Department of Health Services (LADHS) who had histologically confirmed PDAC, CCA, or GBCA and low CA 19-9 values at diagnosis, comparing them with patients who presented with either normal or increased CA 19-9. LADHS, the second-largest municipal health network in the United States, serves primarily minority populations that are rarely represented in existing research.

Materials and Methods

Study population

A system-wide LADHS database was queried for individuals seen at Olive View–UCLA Medical Center (OVMC) and Harbor–UCLA Medical Center (HUMC), both in Los Angeles, CA, USA, whose records contained ICD-10-CM codes corresponding to PBMs **(Table 1)**. Patient files were reviewed manually, and only those with histologic confirmation of PBMs diagnosed between 2014 and 2020 were retained. Exclusions were applied to cases without tissue confirmation or without a recorded CA 19-9 measurement within 30 days of diagnosis.

Table 1. 2021 ICD-10 code set used for disease classification.

ICD-10 Code	Corresponding Disease Classification
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C25	Malignant neoplasm of pancreas
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of the body of the pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of the pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
D01.5	Carcinoma in situ of liver, gallbladder, and bile ducts

Study variables and primary outcome

From the clinical charts, we collected a broad set of demographic and medical details: age, biological sex, ethnic background, body mass index (BMI), tobacco use history, prior non-GI malignancies, and comorbid conditions including diabetes mellitus, hypertension, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, and stroke. Information on whether treatment was delivered with curative or palliative goals was also obtained. Laboratory findings at the point of diagnosis included CA 19-9, total bilirubin, carcinoembryonic antigen, and CA 125 levels [26, 27]. The cancer stage at diagnosis and the Eastern Cooperative Oncology Group (ECOG) performance score were likewise extracted. The main study endpoint—overall survival—referred to the interval between the diagnostic date and either death or the most recent documented follow-up.

CA 19-9 assays and p0atient grouping

Between 2014 and 2020, two automated platforms were used to measure CA 19-9: the ADVIA Centaur system (Bayer Diagnostics, Tarrytown, NY, USA) and the Elecsys E170 analyzer (Roche Diagnostics, Indianapolis, IN, USA). Their analytical detection limits were <2 or ≤3 U/mL. Based on CA 19-9 levels at diagnosis, patients were divided into three predefined categories:

1. Low: ≤3 U/mL
2. Normal: 4–35 U/mL
3. High: >35 U/mL

Statistical analysis

For each CA 19-9 category, descriptive summaries were generated. Survival distributions were approximated using Kaplan–Meier methodology, with differences evaluated through Cox proportional hazards regression.

Median duration of follow-up was determined via the reverse Kaplan–Meier technique. A significance threshold of $p < 0.05$ was applied. All analyses were conducted using Stata/IC 16.1 (StataCorp, College Station, TX, USA).

Results and Discussion

Characteristics of the study sample

A total of 421 individuals were initially identified using 12 ICD-10-CM codes for PBM **(Table 1)**. After excluding those without biopsy-confirmed PDAC, CCA, or GBCA, and those with no recorded CA 19-9 at diagnosis, 283 remained for analysis. Within this cohort, 23 (8.1%) belonged to the low-CA 19-9 category, 70 (24.7%) fell into the normal range, and 190 (67.1%) exhibited elevated values. **Table 2** lists demographic profiles stratified by CA 19-9 group, including age, gender, BMI, race, and smoking status (never, former, or current). Additional abstracted data included previous cancers and comorbidities such as diabetes, hypertension, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, and stroke. Across the three CA 19-9 strata, Hispanic individuals represented the majority (65.2%, 77.1%, and 54%), women were more common (60.9%, 57.1%, and 51.6%), and most had never smoked (82.6%, 72.5%, and 60.5%). Median ages were 60, 62, and 61 years in the low, normal, and high groups, respectively.

Table 2. Comparison of patients with low/undetectable CA 19-9 versus those with normal or elevated values. *No statistically meaningful group differences were observed.*

Characteristic	Low CA 19-9 (n = 23)	Normal CA 19-9 (n = 70)	Elevated CA 19-9 (n = 190)
Age at diagnosis (years), median (IQR)	60 (52–69)	62 (53–70)	61 (55–66)
Male, n (%)	9 (39.1%)	30 (42.9%)	92 (48.4%)
BMI, median (IQR)	26.0 (23.2–30.6)	25.3 (22.4–28.7)	25.4 (22.2–29.9)
Race, n (%)			
Caucasian	3 (13.0%)	5 (7.1%)	31 (16.4%)
Hispanic	15 (65.2%)	54 (77.1%)	102 (54.0%)
Asian	2 (8.7%)	4 (5.7%)	21 (11.1%)
African American	2 (8.7%)	4 (5.7%)	15 (7.9%)
Middle Eastern/North African	0 (0.0%)	1 (1.4%)	2 (1.1%)
Other	1 (4.4%)	2 (2.9%)	18 (9.5%)
Comorbidities			
None	6 (26.1%)	23 (32.9%)	54 (28.4%)
Diabetes	9 (39.1%)	28 (40.0%)	78 (41.1%)
Hypertension	9 (39.1%)	31 (44.3%)	93 (49.0%)
Congestive heart failure	0 (0.0%)	3 (4.3%)	8 (4.2%)
Coronary artery disease	1 (4.4%)	5 (7.1%)	11 (5.8%)
COPD	0 (0.0%)	0 (0.0%)	8 (4.2%)
Cerebrovascular accident	0 (0.0%)	1 (1.4%)	8 (4.2%)
History of other cancer, n (%)			
None	21 (91.3%)	61 (88.4%)	175 (92.1%)
Non-GI	2 (8.7%)	5 (7.2%)	12 (6.3%)
GI	0 (0.0%)	4 (5.8%)	3 (1.6%)
Smoking history, n (%)			
Never	19 (82.6%)	50 (72.5%)	113 (60.1%)
Former	1 (4.4%)	14 (20.3%)	47 (25.0%)
Current	3 (13.0%)	5 (7.3%)	28 (14.9%)

p-values omitted as there were no significant differences between groups. Abbreviations: BMI: Body mass index; GI: gastrointestinal; IQR: interquartile range.

Oncologic profile

Table 3 outlines tumor-related characteristics across CA 19-9 groups, with interquartile ranges in parentheses. Diagnostic CA 19-9 concentrations spanned from 0 to 4,270,000 U/mL. PDAC accounted for the majority of diagnoses (60.9%, 55.7%, and 69%). ECOG performance status of 0 occurred in 40.9%, 64.3%, and 48.7%, while stage IV disease at presentation was seen in 52.2%, 40%, and 50.5% of the low, normal, and high groups. Curative-

intent therapy was most frequent in the normal category (54.3%), whereas palliative treatment predominated in the low (65.2%) and elevated (76.8%) categories. Metastatic disease at diagnosis occurred in 12 (52.2%), 28 (40%), and 96 (50.5%) individuals in the three groups.

Table 3. Tumor characteristics in low/undetectable versus measurable CA 19-9 cohorts.

Characteristic	Low CA 19-9 (n = 23)	Detectable but Normal CA 19-9 (n = 70)	Elevated CA 19-9 (n = 190)	p-Value
CA 19-9 level at diagnosis, median (IQR)	2.0 (2.0–3.0)	16.5 (9.0–22.0)	532.5 (147.0–3469.0)	0.595
CEA level at diagnosis, median (IQR)	4.9 (2.8–6.6)	2.0 (1.4–5.1)	4.1 (1.9–17.8)	0.508
CA 125 level at diagnosis, median (IQR)	30.6 (6.1–55.0)	26.7 (10.4–48.9)	61.3 (20.9–219.0)	0.646
Total bilirubin at diagnosis, median (IQR)	0.6 (0.5–4.0)	1.0 (0.6–2.1)	1.7 (0.8–8.6)	0.002
Organ system with malignancy, n (%)				0.054
Cholangiocarcinoma	5 (21.7%)	18 (25.7%)	46 (24.2%)	
Gallbladder adenocarcinoma	4 (17.4%)	13 (18.6%)	13 (6.8%)	
Pancreatic adenocarcinoma	14 (60.9%)	39 (55.7%)	131 (69.0%)	
Deceased by end of study period, n (%)	12 (52.2%)	32 (45.7%)	120 (63.2%)	0.035
Survival time, median*	1016	1096	344	-
Follow-up time, median*	815	1243	662	-
ECOG at time of diagnosis, n (%)				0.236
0	9 (40.9%)	45 (64.3%)	90 (48.7%)	
1	7 (31.8%)	17 (24.3%)	54 (29.2%)	
2	4 (18.2%)	5 (7.1%)	17 (9.2%)	
3	2 (9.1%)	2 (2.9%)	22 (11.9%)	
4	0 (0.0%)	1 (1.4%)	2 (1.1%)	
Stage at time of diagnosis, n (%)				0.017
I	4 (17.4%)	19 (27.1%)	21 (11.1%)	
II	4 (17.4%)	17 (24.3%)	34 (17.9%)	
III	3 (13.0%)	6 (8.6%)	39 (20.5%)	
IV	12 (52.2%)	28 (40.0%)	96 (50.5%)	
Underwent curative treatment, n (%)	8 (34.8%)	38 (54.3%)	44 (23.2%)	<0.001
Type of treatment, n (%)				<0.001
Chemotherapy	12 (52.2%)	20 (28.6%)	92 (48.4%)	
Surgery	3 (13.0%)	16 (22.9%)	14 (7.4%)	
Chemotherapy and surgery	5 (21.7%)	26 (37.1%)	36 (19.0%)	
Hospice	3 (13.0%)	6 (8.6%)	43 (22.6%)	
None or lost to follow-up	0 (0.0%)	2 (2.9%)	5 (2.6%)	

* Obtained from the Kaplan–Meier estimate of the survivor function. ** Obtained using the reverse Kaplan–Meier estimator. Abbreviations: CEA: Carcinoembryonic antigen; CA 125: cancer antigen 125; ECOG: Eastern Cooperative Oncology Group performance status; IQR: interquartile range.

Survival analysis

Survival findings appear in **Figure 1** and **Tables 3 and 4**. Over a median follow-up of 2.2 years, 164 participants (57.9%) had died. Deaths within each CA 19-9 category totaled 12 (52.1%), 32 (45.7%), and 120 (63.1%). After adjusting for sex, age, BMI, presence of metastasis, and receipt of curative-intent therapy, the hazard of death relative to the low-CA 19-9 group was 1.254 ($p = 0.510$, 95% CI 0.640–2.458) for the normal group and 1.993 ($p = 0.025$, 95% CI 1.089–3.648) for the elevated group **(Table 4)**. Metastatic presentation significantly increased mortality risk (HR = 1.815, $p = 0.002$, CI 1.252–2.629), while curative-intent treatment markedly reduced it (HR = 0.213, $p < 0.001$, CI 0.127–0.356).

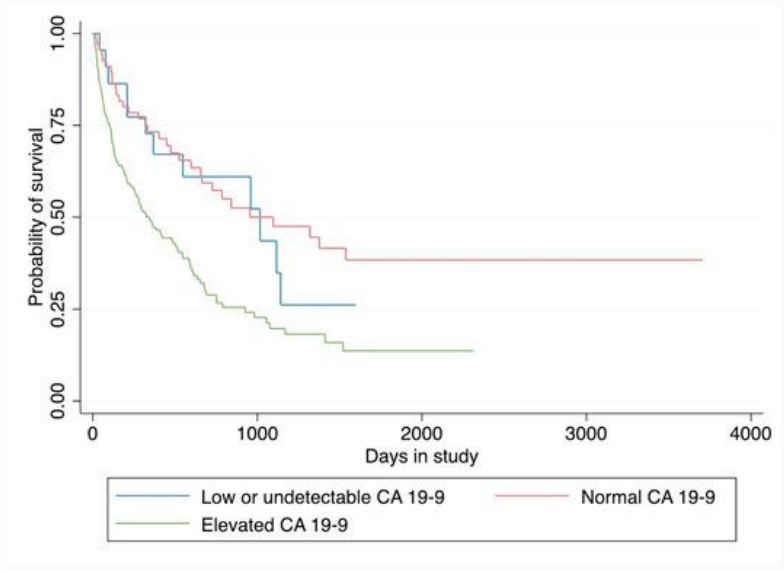

Figure 1. Kaplan–Meier survival curves by CA 19-9 category.

Table 4. Cox regression model for predictors of survival.

Predictor	Hazard Ratio	p-Value	95% Confidence Interval
CA 19-9 level			
Undetectable (reference)	-	-	-
Normal	1.254	0.510	0.640–2.458
Elevated	1.993	0.025*	1.089–3.648
Male	0.973	0.866	0.709–1.336
Age	1.016	0.052	1.000–1.033
BMI	1.001	0.923	0.977–1.026
Evidence of metastases at diagnosis	1.815	0.002*	1.252–2.629
Underwent curative treatment	0.213	<0.001*	0.127–0.356

* Denotes statistical significance.

Discussion

In this investigation, we analyzed clinical characteristics and outcomes among individuals with histologically confirmed PDAC, CCA, or GBCA who presented with low, normal, or elevated CA 19-9 concentrations. This work represents only the second known study specifically focused on patients with PBMs who exhibit low or undetectable CA 19-9 values. Within the LADHS system, we identified 286 patients with tissue-confirmed PBMs; among them, 8.1% had low CA 19-9 readings and 24.7% had values within the normal range at the time of diagnosis. Because PBMs are associated with aggressive biology, limited therapeutic responses, and a tendency to present at advanced stages, clarifying the clinical patterns of individuals whose CA 19-9 levels are unexpectedly low is highly relevant to patient management [28, 29].

CA 19-9 was first recognized as a potential marker for hepatobiliary cancers in 1979, when Koprowski and colleagues isolated an antigen using monoclonal antibodies originally derived from colorectal tumor tissue. It was later observed to also correlate with pancreatic cancer biology [19, 30]. The development of a radioimmunometric assay in 1983 by Del Villano *et al*. enabled accurate measurement of CA 19-9 with strong diagnostic performance for PBMs [31]. Since then, this biomarker has become entrenched in clinical practice for diagnostic evaluation, prognosis estimation, and treatment monitoring. However, its interpretation must account for important limitations: elevations can occur in a range of other malignancies (such as ovarian or endometrial cancers) and in benign conditions like biliary obstruction or chronic pancreatitis. Additionally, a subset of patients inherently produces little or no CA 19-9, complicating its clinical interpretation.

A substantial body of literature has evaluated CA 19-9 in relation to tumor burden, surgical resectability, and survival outcomes. For instance, a study from Massachusetts General Hospital assessed how preoperative CA 19-9 aligned with pathological cancer staging in 176 patients who had both pre- and postoperative measurements.

Higher preoperative CA 19-9 values corresponded with more advanced disease stages, and concentrations tended to be lower in lymph-node–negative cases [32]. Multiple groups have likewise explored how the marker relates to resectability. One study demonstrated that CA 19-9 values were significantly lower in resectable PDAC compared with unresectable disease [33]. Another analysis of 262 individuals undergoing staging laparoscopy identified that preoperative CA 19-9 ≥130 U/mL predicted unresectability on multivariate modeling (HR 2.70, $p = 0.005$) [34].

CA 19-9 has also been linked to treatment responsiveness and the trajectory of disease under therapy. In a cohort of 43 PDAC patients, changes in CA 19-9 before and after chemotherapy were associated with survival outcomes: individuals with >20% decline in their baseline CA 19-9 after 8 weeks of therapy experienced significantly longer median survival than those with increases or declines below 20% [35]. A study from Italy evaluating stage III–IV pancreatic adenocarcinoma similarly found that baseline CA 19-9 levels independently correlated with survival, and reductions exceeding 89% after chemotherapy were associated with markedly longer median survival times relative to patients whose declines fell between 50–80% or those with <50% reductions or increases [36].

The biomarker has also been extensively researched as a direct predictor of overall survival. Prior studies have shown that patients with PBMs and normal CA 19-9 values (<37 U/mL) at diagnosis tend to have better prognoses [32, 37, 38]. A Japanese investigation involving 117 pancreatic cancer patients demonstrated a 5-year disease-specific survival rate of 60% among those with normal CA 19-9, in contrast to just 4% among individuals with levels above 37 U/mL [39]. Another study comparing patients with CA 19-9 ≤120 U/mL to those with values >120 U/mL revealed significantly superior 1-, 3-, and 5-year survival for the ≤120 U/mL group ($p = 0.002$) [40]. Postoperative CA 19-9 levels have also been informative: PDAC patients with postresection CA 19-9 >90 U/mL showed a dramatically increased mortality risk (HR 3.34; $p < 0.0001$) compared with those with ≤90 U/mL [41]. A separate Japanese cohort of 269 patients demonstrated that CA 19-9 levels >37 U/mL after surgery predicted inferior survival ($p < 0.0001$), and elevated postoperative levels were more common when margins were positive ($p = 0.02$) [42].

Interpretation of CA 19-9 is further complicated by biological variability. Approximately 5–10% of individuals carry a Lewis-negative phenotype and therefore do not synthesize the CA 19-9 antigen at all, even in the presence of metastatic PBMs [11, 43, 44]. Because CA 19-9 is a sialyl Lewis antigen, those lacking the sialyl Lewis structure do not express the enzyme 1,4-fucosyl transferase required for its production. Consequently, these patients may appear to have normal or even undetectable CA 19-9 despite harboring advanced disease, obscuring the true prognostic interpretation of their tumor marker profile.

In this investigation, we examined individuals whose CA 19-9 values were low or non-measurable and compared them with those whose CA 19-9 levels were within the normal range or elevated. Because the study design was retrospective, we were unable to determine Lewis antigen phenotypes; nevertheless, 8.1% of the cohort exhibited low CA 19-9 concentrations, a proportion comparable to published estimates for Lewis-negative groups. Within our predominantly Hispanic LADHS sample, most patients across all three CA 19-9 categories were diagnosed at stage IV, reflecting the commonly late clinical presentation and substantial burden associated with PBMs [26, 27]. Moreover, after adjusting for sex, age, BMI, metastatic disease, and receipt of curative-intent therapy, elevated CA 19-9 was linked to a markedly higher risk of mortality when contrasted with the low-CA-19-9 subgroup. No meaningful difference in mortality risk was observed between the normal-level group and the low-level group. These results parallel the findings of A.C. Berger *et al*., who assessed 129 pancreatic cancer cases from the Fox Chase Cancer Center and reported that survival among patients with low and normal CA 19-9 levels did not differ, yet both groups outperformed those with elevated levels [45]. A broader, multi-institutional study with a larger sample may clarify any nuanced survival differences between low and normal CA 19-9 categories.

One of the notable advantages of this project is its size and focus: few studies have examined low CA 19-9 cases within a primarily Hispanic safety-net population. Although many reports evaluate CA 19-9 behavior in pancreaticobiliary cancers, they seldom isolate patients with low or undetectable levels. In addition, much of the prior research centers on populations unlike the LADHS cohort, such as East Asian or European groups. According to U.S. Census data, LADHS represents the county with the highest Hispanic population nationwide. Considering the persistent underrepresentation of racial and ethnic minorities in clinical studies—and the documented disparities in pancreatic cancer incidence and survival across groups [46]—the current study addresses an essential gap. It also provides detailed demographic and oncologic characterization for each category, including CEA and CA 125 biomarkers, ECOG performance scores, initial tumor stage, and treatment modalities.

Several limitations merit discussion. First, the project relied on retrospective chart review. Second, CA 19-9 measurements were not standardized to a single assay; both the ADVIA Centaur and Elecsys E170 platforms were used between 2014 and 2020 within LADHS. One defined undetectable CA 19-9 as <2 U/mL, whereas the other used ≤3 U/mL, though both considered 35 U/mL as the upper limit of normal. Third, although the 8.1% rate of low or non-detectable CA 19-9 aligns with the 5–10% estimate of Lewis antigen-negative prevalence, individual Lewis phenotypes were not assessed in our cohort.

Conclusion

To date, only a limited number of investigations have concentrated on patients with low or undetectable CA 19-9, particularly in the context of GBCA, CCA, and PDAC. This study expands the modest existing literature on PBM patients with low CA 19-9, an issue of importance given the high morbidity and fatality rates associated with these tumors. We demonstrated that individuals with low CA 19-9 exhibit significantly reduced mortality risk compared with those whose levels are elevated, despite the challenges of tracking disease activity in this subgroup. Both elevated CA 19-9 and metastatic spread correlated with increased mortality hazard, whereas curative-intent treatment correlated with reduced hazard. Additional multicenter investigations are required to further clarify the clinical implications of low or undetectable CA 19-9 and to identify optimal management strategies for this patient population.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.
3. National Cancer Institute. Cancer Stat Facts: Pancreatic Cancer. Surveillance, Epidemiology, and End Results Program (SEER). 2021. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html (accessed 26 December 2022).
4. Cheng H, Luo G, Lu Y, Jin K, Guo M, Xu J, et al. The combination of systemic inflammation-based marker NLR and circulating regulatory T cells predicts the prognosis of resectable pancreatic cancer patients. Pancreatology. 2016;16(6):1080-4.
5. Sohal DP, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34(23):2784-96.
6. Rosen A, Linder S, Harmenberg U, Pegert S. Serum levels of CA 19-9 and CA50 in relation to Lewis blood cell status in patients with malignant and benign pancreatic disease. Pancreas. 1993;8(2):160-5.
7. Molina R, Ojeda B, Filella X, Borras G, Jo J, Mas E, et al. A prospective study of tumor markers CA 125 and CA 19.9 in patients with epithelial ovarian carcinomas. Tumour Biol. 1992;13(4):278-86.
8. Cherchi PL, Dessole S, Ruiu GA, Ambrosini G, Farina M, Capobianco G, et al. The value of serum CA 125 and association CA 125/CA 19-9 in endometrial carcinoma. Eur J Gynaecol Oncol. 1999;20(4):315-7.
9. Molina R, Auge JM, Escudero JM, Marrades R, Viñolas N, Carcereny E, et al. Mucins CA 125, CA 19.9, CA 15.3 and TAG-72.3 as tumor markers in patients with lung cancer: comparison with CYFRA 21-1, CEA, SCC and NSE. Tumour Biol. 2008;29(5):371-80.
10. Duffy MJ, Sturgeon C, Lamerz R, Haglund C, Holubec VL, Klapdor R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol. 2010;21(3):441-7.

11. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol. 2012;3(2):105-19.
12. Furuya N, Kawa S, Hasebe O, Tokoo M, Mukawa K, Maejima S, et al. Comparative study of CA 242 and CA19-9 in chronic pancreatitis. Br J Cancer. 1996;73(3):372-6.
13. Barone D, Onetto M, Conio M, Paganuzzi M, Saccomanno S, Aste H, et al. CA 19-9 assay in patients with extrahepatic cholestatic jaundice. Int J Biol Markers. 1988;3(2):95-100.
14. Peterli R, Meyer-Wyss B, Herzog U, Tondelli P. CA 19-9 has no value as a tumor marker in obstructive jaundice. Schweiz Med Wochenschr. 1999;129(3):77-9.
15. Akdoğan M, Saşmaz N, Kayhan B, Biyikoğlu I, Dişibeyaz S, Sahin B. Extraordinarily elevated CA 19-9 in benign conditions: a case report and review of the literature. Tumori. 2001;87(5):337-9.
16. Vestergaard EM, Hein HO, Meyer H, Grunnet N, Jørgensen J, Wolf H, et al. Reference values and biological variation for tumor marker CA 19-9 in serum for different Lewis and secretor genotypes. Clin Chem. 1999;45(1):54-61.
17. Henrikson NB, Bowles EJA, Blasi PR, Morrison CC, Nguyen M, Pillarisetty VG, et al. Screening for Pancreatic Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality; 2019. Report No.: 19-05241-EF-1.
18. Parra-Ramírez M, Santos VM, Canis SM, Pla XF, Fradera JMA, Porto RF. Relationship between CA 19.9 and the Lewis phenotype: options to improve diagnostic efficiency. Anticancer Res. 2018;38(10):5883-8.
19. Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, et al. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med. 2013;13(3):340-51.
20. Wu H, Guo JC, Yang SH, Tien YW, Kuo SH. Postoperative imaging and tumor marker surveillance in resected pancreatic cancer. J Clin Med. 2019;8(8):1115.
21. Motoi F, Murakami Y, Okada KI, Matsumoto I, Uemura K, Satoi S, et al. Sustained elevation of postoperative serum level of carbohydrate antigen 19-9 is high-risk stigmata for primary hepatic recurrence…. World J Surg. 2019;43(2):634-41.
22. Rieser CJ, Zenati M, Hamad A, Abbas AIA, Bahary N, Zureikat AH, et al. CA19-9 on postoperative surveillance in pancreatic ductal adenocarcinoma: predicting recurrence and changing prognosis over time. Ann Surg Oncol. 2018;25(11):3483-91.
23. George B, Kent M, Surinach A, Lamarre N, Cockrum P. The association of real-world CA 19-9 level monitoring patterns and clinical outcomes among patients with metastatic pancreatic ductal adenocarcinoma. Front Oncol. 2021;11:754687.
24. Shin K, Jung EK, Park SJ, Jeong S, Kim IH, Lee MA. Neutrophil-to-lymphocyte ratio and carbohydrate antigen 19-9 as prognostic markers for advanced pancreatic cancer patients receiving first-line chemotherapy. World J Gastrointest Oncol. 2021;13(9):915-28.
25. Tomishima K, Ishii S, Fujisawa T, Ikemura M, Ota H, Kabemura D, et al. Duration of reduced CA19-9 levels is a better prognostic factor than its rate of reduction for unresectable locally advanced pancreatic cancer. Cancers (Basel). 2021;13(17):4224.
26. Duraker N, Hot S, Polat Y, Höbek A, Gençler N, Urhan N. CEA, CA 19-9, and CA 125 in the differential diagnosis of benign and malignant pancreatic diseases with or without jaundice. J Surg Oncol. 2007;95(2):142-7.
27. Safi F, Roscher R, Bittner R, Schenkluhn B, Dopfer HP, Beger HG. High sensitivity and specificity of CA 19-9 for pancreatic carcinoma in comparison to chronic pancreatitis. Pancreas. 1987;2(4):398-403.
28. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis. 2010;28(4-5):645-56.
29. Li J, Merl MY, Chabot J, Saif MW. Updates of adjuvant therapy in pancreatic cancer: where are we and where are we going? JOP. 2010;11(4):310-2.
30. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. Somat Cell Genet. 1979;5(6):957-71.
31. Del Villano BC, Brennan S, Brock P, Bucher C, Liu V, McClure M, et al. Radioimmunometric assay for a monoclonal antibody-defined tumor marker, CA 19-9. Clin Chem. 1983;29(3):549-52.

32. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-del Castillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol. 2006;24(18):2897-902.
33. Kilic M, Gocmen E, Tez M, Ertan T, Keskek M, Koc M. Value of preoperative serum CA 19-9 levels in predicting resectability for pancreatic cancer. Can J Surg. 2006;49(4):241-4.
34. Maithel SK, Maloney S, Winston C, Gonen M, D'Angelica MI, DeMatteo RP, et al. Preoperative CA 19-9 and the yield of staging laparoscopy in patients with radiographically resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2008;15(11):3512-20.
35. Halm U, Schumann T, Schiefke I, Witzigmann H, Mössner J, Keim V. Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. Br J Cancer. 2000;82(5):1013-6.
36. Reni M, Cereda S, Balzano G, Passoni P, Rognone A, Fugazza C, et al. Carbohydrate antigen 19-9 change during chemotherapy for advanced pancreatic adenocarcinoma. Cancer. 2009;115(12):2630-9.
37. Kondo N, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, et al. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol. 2010;17(8):2321-9.
38. Nakao A, Oshima K, Nomoto S, Takeda S, Kaneko T, Ichihara T, et al. Clinical usefulness of CA-19-9 in pancreatic carcinoma. Semin Surg Oncol. 1998;15(1):15-22.
39. Waraya M, Yamashita K, Katagiri H, Ishii K, Takahashi Y, Furuta K, et al. Preoperative serum CA19-9 and dissected peripancreatic tissue margin as determiners of long-term survival in pancreatic cancer. Ann Surg Oncol. 2009;16(5):1231-40.
40. Barton JG, Bois JP, Sarr MG, Wood CM, Qin R, Thomsen KM, et al. Predictive and prognostic value of CA 19-9 in resected pancreatic adenocarcinoma. J Gastrointest Surg. 2009;13(11):2050-8.
41. Berger AC, Garcia M Jr, Hoffman JP, Regine WF, Abrams RA, Safran H, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. J Clin Oncol. 2008;26(34):5918-22.
42. Hata S, Sakamoto Y, Yamamoto Y, Nara S, Esaki M, Shimada K, et al. Prognostic impact of postoperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol. 2012;19(2):636-41.
43. Kim HJ, Kim MH, Myung SJ, Lim BC, Park ET, Yoo KS, et al. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. Am J Gastroenterol. 1999;94(7):1941-6.
44. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 2007;33(3):266-70.
45. Berger AC, Meszoely IM, Ross EA, Watson JC, Hoffman JP. Undetectable preoperative levels of serum CA 19-9 correlate with improved survival for patients with resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2004;11(7):644-9.
46. Herremans KM, Riner AN, Winn RA, Trevino JG. Diversity and inclusion in pancreatic cancer clinical trials. Gastroenterology. 2021;161(6):1741-6.