Predictive Factors for Elevated Postoperative Carbohydrate Antigen 19-9 Levels in Patients With Resected Pancreatic Cancer

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Abstract. *Aim: In this study, we investigated the clinical significance of postoperative serum carbohydrate antigen (CA) 19-9 in patients with pancreatic ductal carcinoma (PDAC). Patients and Methods: A series of 116 patients with macroscopically curative PDAC resection was retrospectively evaluated. The cut-off level for elevated postoperative CA 19-9 was 37 U/ml. Results: Patients with high postoperative CA19-9 levels had a significantly poorer prognosis than patients with normal postoperative CA19-9 levels, as revealed by the log-rank test. Multivariate analysis identified R1 resection and preoperative serum CA19-9 level ≥ 400 U/ml independently predicted elevated postoperative CA 19-9 levels. R1 resection and preoperative serum CA19-9 ≥ 400 U/ml were significantly associated with the recurrence of peritoneal dissemination and hepatic metastasis, respectively, within one year of operation. Conclusion: Elevated postoperative serum CA 19-9 level was associated with a poor prognosis and reflected positive resection margins and high preoperative CA 19-9 levels, which indicated presence of occult distant metastasis in patients with PDAC.*

Pancreatic ductal adenocarcinoma (PDAC) is highly lethal, and surgical resection is the only curative treatment available. The 5-year survival of patients with curative resection of PDAC has been estimated to be 20% (1). Adjuvant and neoadjuvant chemotherapies are offered in clinical practice aiming to improve survival (2-6). Accurate prediction of prognosis and effective stratification are important for planning postsurgical treatment and designing clinical trials. The prognostic value of carbohydrate antigen

(CA) 19-9 has been evaluated in patients with PDAC following curative resection, and it reportedly reflects tumor burden (7, 8). High postoperative serum (Post)-CA 19-9 levels have been reported as a prognostic factor, and elevated Post-CA 19-9 levels were reported to be a more powerful prognostic factor than preoperative serum (Pre)-CA 19-9 (9-11) level. High Post-CA 19-9 levels have been considered to be associated with microscopically positive surgical margin or occult distant metastasis; however, their relationship has not been adequately and statistically confirmed yet (10-12). In the present study, we aimed to investigate the clinical significance of elevated Post-CA 19-9 levels by analyzing which factors are predictive of elevated Post-CA 19-9 levels.

Patients and Methods

Patient population and study design. This retrospective cohort study evaluated patient data collected at the Tochigi Cancer Center. The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution (Approval No. C-200) and it conforms to the provisions of the Declaration of Helsinki.

A series of 166 patients with surgical resection for PDAC between January 2008 and December 2016 were included in the analysis. Eleven patients with macroscopically positive resection margin or distant metastasis were excluded. Further, Pre-CA 19-9 was measured within 6 weeks of surgery. The lowest serum CA19-9 level within 3 months after surgery was adopted as the Post-CA 19-9 level. We did not refer CA 19-9 value after initiation of adjuvant chemotherapy. Twenty-one patients with Pre-CA 19-9 < 5 U/ml were excluded because they were considered nonsecreters. CA 19-9 values were not included in the analysis if serum total bilirubin was ≥ 2.0 mg/dl at the time of assay. Eighteen patients were also excluded because their Pre- or Post-CA 19-9 levels were unavailable. Finally, the remaining 116 patients were enrolled in the study.

The patients were stratified based on their Post-CA 19-9 levels into groups below or above the 37 U/ml reference upper limit of normal. The normal Post-CA 19-9 group included patients with concentrations ≤ 37 U/ml, whereas the elevated Post-CA 19-9 group included those with concentrations > 37 U/ml. Additional patient variables included in the analysis were age, sex, resectable status, preoperative treatment, operative method, combined resection of the

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portal vein (PV) or celiac artery (CA), histological grade, pathological tumor and node stage, resection margin status, and perioperative chemotherapy administration. Pathological tumor and node stage were classified using the criteria described in the Union for International Cancer Control (UICC) eighth edition (12).

Statistical analysis. Continuous variables are expressed as medians and interquartile range (IQR). Comparisons of the values of patient variables in the normal and elevated Post-CA 19-9 groups were performed with the Mann–Whitney *U*-test and Fisher’s exact test, as appropriate. Overall survival (OS) was defined as the time from the date of surgery to either death from any cause or the last follow-up. Patients alive at the last follow-up were censored. The survival of patients with normal and elevated Post-CA 19-9 levels was estimated by the Kaplan–Meier method and compared by log-rank test.

Univariate and multivariate logistic regression analysis were used to identify factors that were independent predictive factors of elevated Post-CA 19-9 level. Factors with *p*-values <0.2 following univariate analysis were included in the multivariate analysis. Because we assumed that Pre- and Post-CA 19-9 levels were related, receiver operating characteristics (ROC) curve analysis was used to define the optimal cut-off value of Pre-CA 19-9 that predicted elevated Post-CA 19-9 level. The optimal cut-off was the value with the maximum sensitivity and specificity. The association of recurrence within one year of operation with Post-CA 19-9 level and independent predictive factors of elevated Post-CA 19-9 level were identified by multivariate analysis. *p*-Values <0.05 were considered statistically significant. The statistical analysis was conducted with the R 3.4.4 statistical package (<https://www.r-project.org>).

Results

Patient characteristics. Fifty-eight of the 116 patients (50%) were males and 58 (50%) were females. Their median age was 69 (IQR 63-76) years, and the median Pre-CA 19-9 was 205 (IQR 49-1191) U/ml. Pancreaticoduodenectomy was performed in 54 patients (47%), total pancreatectomy in 7 (6%), and distal pancreatectomy in 55 (47%). PV resection was performed in 39 (34%) and celiac artery (CA) resection in 6 (5%). The histological characteristics included 5 patients (4%) with UICC grade G1, 96 (83%) with grade G2, and 15 (13%) with grade G3 tumors. Thirteen patients (11%) were stage T1, 56 (48%) were stage T2, 43 (37%) were stage T3, and 4 (3.4%) were stage T4. Twenty-nine (25%) were stage N0, 45 (39%) were stage N1, and 42 (36%) were stage N2. Surgery achieved R0 resection in 102 patients (88%) and R1 resection in 14 (12%). The median Post-CA 19-9 level was 30 (IQR 10-202) U/ml, and 84 patients (72%) received adjuvant chemotherapy. Of these patients, 61 (73%) received S-1 monotherapy, 21 (25%) received gemcitabine monotherapy, and 2 (2%) received gemcitabine plus S-1 therapy. Further, 1-, 3-, and 5-year OS were 75.8%, 35.2%, and 22.3%, respectively; median survival was 23.1 (range 1.5-107) months.

Normal and elevated Post-CA 19-9 levels. As shown in Table I, 62 patients (53%) had a normal Post-CA 19-9 level and 54 (47%) had elevated Post-CA 19-9 level. Patients with elevated

Table I. Comparison between patients with normal and elevated serum Post-CA19-9.

	Postoperative CA19-9		<i>p</i> -Value
	≤37U/ml	>37U/ml	
Number of patients	62	54	
Male gender	33 (54)	25 (46)	0.57
Age, years	66 (61-72)	72 (65-77)	0.010
Preoperative serum CA19-9, U/ml	73 (26-298)	658 (191-3195)	<0.001
Resectability status			
R	42 (68)	31 (57)	0.34
BR	20 (32)	23 (43)	
Operative method			0.22
PD	25 (40)	29 (54)	
TP	3 (5)	4 (7)	
DP	34 (55)	21 (39)	
Vascular resection			0.029
PV	15 (24)	24 (44)	
CA	3 (5)	3 (6)	1.00
Histological grade			0.42
G1	4 (7)	1 (2)	
G2	49 (79)	47 (87)	
G3	9 (14)	6 (11)	
Tumor stage (UICC 8th ed.)			0.60
T1	9 (15)	4 (7)	
T2	30 (48)	26 (48)	
T3	21 (34)	22 (41)	
T4	2 (3)	2 (4)	
Node stage (UICC 8th ed.)			<0.001
N0	22 (36)	7 (13)	
N1	27 (43)	18 (33)	
N2	13 (21)	29 (54)	
Surgical margin status			<0.001
R0	60 (97)	42 (78)	
R1	2 (3)	12 (22)	
Postoperative serum CA19-9, U/mL	10 (6-16)	242 (66-904)	<0.001
Adjuvant chemotherapy			0.90
S-1	35 (57)	26 (48)	
GEM	13 (21)	8 (15)	
S-1 + GEM	1 (1)	1 (2)	
Preoperative treatment			0.41
GEM	0	1 (2)	
S-1 + GEM	4 (7)	4 (7)	
GEM + nabPTX	0	2 (4)	
FOLFIRINOX	2 (3)	0	
S-1 + RTx	1 (2)	2 (4)	

CA 19-9: Carbohydrate antigen 19-9; PD: pancreaticoduodenectomy; TP: total pancreatectomy; DP: distal pancreatectomy; PV: portal vein; CA: celiac axis; UICC Union for International Cancer Control; GEM gemcitabine; nabPTX nanoparticle albumin-bound paclitaxel; FOLFIRINOX combination of bolus and infusional fluorouracil, leucovorin, irinotecan and oxaliplatin. Data are expressed as median (interquartile range) or n (%).

Post-CA 19-9 levels were older (*p*=0.01), and their Pre-CA 19-9 levels were higher (*p*<0.001) than that in patients with

Figure 1. Overall survival of patients with normal and elevated serum Post-CA 19-9 levels.

normal Post-CA 19-9 levels. The PV resection ($p=0.029$) and R1 resection ($p<0.001$) rates were significantly higher in patients with elevated levels than in those with normal Post-CA 19-9 levels. The tumor stage in the two groups was not significantly different, but the distribution of node stage was significantly different ($p<0.001$). Median Post-CA 19-9 level was 10 (IQR=6-16) U/ml in patients with normal Post-CA 19-9 levels and 242 (IQR 66-904) U/ml in those with elevated Post-CA 19-9 levels ($p<0.001$).

The Kaplan–Meier analysis of OS in patients with normal and elevated Post-CA 19-9 is shown in Figure 1. One-, 3-, and 5-year OS and median survival time were significantly better in the normal (92%, 57%, 31%, and 39.7 months) than in the elevated (57%, 10%, 10%, and 14.0 months) Post-CA 19-9 group ($p<0.001$).

Factors predictive of elevated Post-CA 19-9. The results of the univariate and multivariate logistic regression analysis of patient preoperative and pathological factors related to elevated postoperative serum CA19-9 levels are shown in Table II. The results of ROC curve analysis of Pre-CA 19-9 to predict elevated Post-CA 19-9 levels are shown in Figure 2. A Pre-CA 19-9 concentration of 396 U/ml was found to be the optimal cut-off value for prediction of an elevated Post-

CA 19-9 level. The sensitivity and specificity of 396 U/ml cut-off level were 67% and 79%, respectively. The area under the ROC curve was 0.760 (95% CI=0.671-0.849). For simplicity, 400 U/ml was adopted as the cut-off value. In univariate analysis, age ($p=0.022$), Pre-CA19-9 ≥ 400 U/ml ($p<0.001$), PV or CA resection ($p=0.014$), N1-N2 node stage ($p=0.007$), and R1 resection ($p=0.009$) were significantly associated with elevated Post-CA 19-9 levels. Multivariate analysis revealed that Pre-CA19-9 ≥ 400 U/ml (odds ratio [OR], 6.41; 95% CI: 2.44-16.8; $p<0.001$) and R1 resection (OR, 17.2; 95% CI: 1.83-161, $p=0.01$) were independent predictive factors for elevated Post-CA 19-9 level.

Early PDAC recurrence. The nature of the first site recurrences within one year of operation that occurred in patients with high and low Post-CA 19-9, Pre-CA 19-9, and R0 or R1 resection are shown in Table III. Recurrence occurred in 66 of the 116 patients within one year of operation. Any observed metastasis ($p<0.001$), hepatic metastasis ($p<0.001$), and peritoneal dissemination ($p=0.020$) were significantly more frequent in patients with elevated levels than with normal Post-CA 19-9 levels. Overall metastasis ($p<0.001$), hepatic metastasis ($p<0.001$), local recurrence ($p=0.049$), and lymph node metastasis ($p=0.039$)

Figure 2. Receiver operating characteristic curve analysis of pre-CA 19-9 levels that predicted elevated Post-CA 19-9 levels.

were significantly higher in patients with a Pre-CA 19-9 ≥ 400 U/ml than in those with Pre-CA 19-9 levels < 400 U/ml. Overall metastasis ($p=0.023$), peritoneal dissemination ($p=0.012$) and local recurrence ($p=0.027$) were more frequent in patients with R1 resection than in those with R0 resection.

Discussion

This retrospective cohort study investigated the factors predictive of elevated Post-CA 19-9 levels after curative resection for PDAC. Multivariate logistic regression showed that a Pre-CA 19-9 level ≥ 400 U/ml and R1 resection were independent prognostic factors for elevated Post-CA 19-9 levels. The patients with elevated Post-CA 19-9 levels were found to have higher rates of recurrence involving hepatic metastasis and peritoneal dissemination than those with normal Post-CA 19-9 levels. R1 resection and a Pre-CA 19-9 level ≥ 400 U/ml were significantly associated with peritoneal dissemination and hepatic recurrence, respectively. The results are consistent with those of previous retrospective cohort studies reporting that high Post-CA 19-9 levels were associated with poor survival in patients with PDAC after resection (9, 10, 13, 14). However, the clinical factors associated with an increased risk of elevated CA 19-

9 levels were not described. In the present study, we identified the clinicopathological characteristics predictive of elevated Post-CA 19-9 levels.

The finding that elevated Post-CA 19-9 levels indicated the prognosis of PDAC patients after macroscopically curative resection is consistent with the findings of previous studies. Optimal Post-CA 19-9 predictive cut-off levels of 37, 90, 180, and 200 U/ml have been reported (7, 9, 10, 13-15). Two reports adopted the lowest p-value obtained by univariate analysis, which were 37 and 200 U/ml (7, 11). Other studies used 70 U/ml, a two-fold elevation of the upper limit of normal (15) or used 35 or 37 U/ml as cut-offs (10, 13, 14). In the present study, a Post-CA 19-9 cut-off level of 37 U/ml had prognostic value. Although the optimal cut-off level was not confirmed statistically, 37 U/ml proved to be a practical and acceptable cut-off point.

In these patients with PDAC, an elevated post-CA 19-9 level was also found to be a serological indicator of positive surgical margins and occult distant metastasis after macroscopically curative resection. Patient age, PV resection, lymph node metastasis, and R1 resection were higher in patients with elevated levels than in those with normal Post-CA 19-9 levels, which is consistent with the findings of previous reports (9, 10, 13, 14). Multivariate analysis showed

Table II. Univariate and multivariate logistic regression analysis of factors related to elevated serum Post-CA19-9.

Variables	Reference/test	Univariate			Multivariate		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Gender	Female/Male	0.75	0.36-1.57	0.45			
Age, y	<70/≥70	1.05	1.01-1.10	0.022	1.70	0.68-4.22	0.26
Preoperative CA19-9, U/mL	<400/≥400	6.94	3.03-15.9	<0.001	6.48	2.53-16.6	<0.001
Operation method	DP/PD or TP	1.91	0.90-4.00	0.087	1.05	0.38-2.84	0.92
Resectability status	R/BR	1.56	0.73-3.32	0.25			
Vascular resection	Not performed/Performed	2.65	1.22-5.73	0.014	2.15	0.78-5.85	0.14
Historological grade	G1-G2/G3	0.73	0.24-2.22	0.58			
Tumor stage (UICC 8th ed.)	T1-T2/T3-T4	1.36	0.64-2.85	0.42			
Node stage (UICC 8th ed.)	N0/N1-N2	3.69	1.43-9.54	0.007	1.60	0.49-5.18	0.43
Intraoperative cytology	negative/positive	1.48	0.38-5.82	0.58			
Surgical margin status	R0/R1	15.6	1.94-125.0	0.009	18.0	1.91-170	0.010
Preoperative treatment	Not performed/Performed	1.57	0.54-4.55	0.40			

OR: Odds ratio; CI: confidence interval; CA 19-9: carbohydrate antigen 19-9; PV: portal vein; CA: celiac axis; PD: pancreaticoduodenectomy; TP: total pancreatectomy; DP: distal pancreatectomy.

Table III. Types of first site recurrence within postoperative one year associated with Post-CA19-9 value, Pre-CA 19-9 value, and R status.

	Postoperative CA19-9			Preoperative CA19-9			R status		
	≤37 U/ml	>37 U/ml	p-Value	≤400 U/ml	>400 U/ml	p-Value	R 0	R 1	p-Value
Number of patients	62	54		68	48		102	14	
Any observed metastasis	20 (32)	46 (85)	<0.001	27 (44)	39 (72)	<0.001	54 (53)	12 (86)	0.023
Hepatic metastasis	7 (11)	29 (54)	<0.001	14 (23)	22 (41)	<0.001	29 (28)	7 (50)	0.12
Peritoneal dissemination	0 (0)	5 (9)	0.020	2 (3)	3 (6)	0.640	2 (2)	3 (21)	0.012
Local recurrence	3 (5)	8 (15)	0.11	3 (5)	8 (15)	0.049	7 (7)	4 (29)	0.027
Lymph node metastasis	5 (8)	8 (15)	0.38	4 (6)	9 (17)	0.039	12 (12)	1 (7)	1.00
Pulmonary metastasis	0 (0)	1 (2)	0.47	0 (0)	1 (2)	0.41	1 (1)	0 (0)	1.00
Other distant metastasis	1 (2)	0 (0)	1.00	1 (2)	0 (0)	1.00	1 (1)	0 (0)	1.00

CA 19-9: Carbohydrate antigen 19-9.

that R1 resection and CA 19-9 level ≥400 U/ml were independent risk factors for elevated Post-CA 19-9 levels. As R1 resection involves a microscopically detectable residual tumor, the finding that R1 resection was associated with peritoneal dissemination and local recurrence is not surprising. Previous studies reported that high Pre-CA19-9 levels reflected occult distant metastasis if no distant metastasis was detected by preoperative imaging and intraoperative probing. Others have reported that serum CA 19-9 levels and tumor burden were correlated. Serum CA 19-9 level is routinely used in clinical practice for diagnosis, prognosis, and monitoring treatment response in PDAC (8, 16). Pre-CA 19-9 level has been associated with the presence of unresectable disease during staging laparotomy (17) and hepatic micrometastasis detected by intraoperative indocyanin green fluorescent imaging (18). In the present study, a Pre-CA 19-9 level ≥400 U/ml was associated with elevated Post-CA 19-9 level and postoperative recurrence as hepatic metastasis. It is

clinically remarkable that elevated Post-CA 19-9 levels reflected Pre-CA 19-9 level ≥400 U/ml as a marker of occult distant metastasis and R1 resection as evidence of locoregional residual tumor.

To the best of our knowledge, the optimal Pre-CA 19-9 cut-off level for predicting elevated Post-CA 19-9 level has not been previously studied. Previous studies found a significant association or trend toward association of elevated Post-CA 19-9 and Pre-CA 19-9 levels (13, 14). In this patient series, ROC curve analysis and the AUC value indicated that Pre-CA 19-9 had good sensitivity, specificity, and accuracy for predicting elevated Post-CA 19-9 levels. The optimal Pre-CA 19-9 cut-off for predicting elevated Post-CA 19-9 level was found to be 400 U/ml. Other studies have reported Pre-CA 19-9 cut-offs with a prognostic value. Unlike Post-CA 19-9 levels, Pre-CA 19-9 level ≥37 U/ml had limited prognostic value (7, 10). The reported cut-off values with prognostic value ranged from 100-2,000 U/ml (7, 19-21). Thus, the predicted Pre-CA 19-9

cut-off level of 400 U/ml is reasonable considering previous reports and is consistent with the finding that elevated Post-CA 19-9 levels were associated with a worse prognosis.

Serum CA 19-9 levels are reportedly useful for perioperative management of patients with PDAC (16, 22), and the results of the present study suggest that patients with elevated Post-CA 19-9 levels are eligible for more intensive adjuvant or organ-specific treatment. Serum CA19-9 level is easy to monitor and has objective value, and prediction of elevated Post-CA19-9 levels can be helpful in selecting previously advocated preoperative treatments (23, 24). In this patient series, high Pre-CA 19-9 levels supported preoperative treatment because of the increased risk of hepatic metastasis. As previously reported Pre- and Post-CA 19-9 cut-off levels vary (7, 19-21), further studies are required to confirm the optimal cut-offs.

The study has certain limitations. These include the small sample size and single-center retrospective study design. As several biases may have affected the results, the findings should be further validated in a different patient series. In addition, occult distant metastasis was not directly evaluated. The evidence that Post-CA 19-9 levels indicated occult distant metastasis was obtained from statistical analysis and was supported by previous reports. The use of diagnostic tools to detect occult distant metastasis might provide definitive evidence of this relationship. Although, intraoperative indocyanin green fluorescent imaging is effective for probing occult hepatic metastasis, it is not effective for finding deep hepatic lesions (18). Development of effective methods for preoperative detection of occult distant metastasis is thus warranted. Moreover, therapeutic strategies using CA 19-9 levels cannot be applicable to all patients with PDAC because some patients with Lewis Antigen negative do not secrete CA 19-9. In addition, the presence of obstructive jaundice can affect CA 19-9 level. Considering these cases, CA19-9 as well as other biomarkers can be useful to improve the treatment strategy for patients with PDAC (25, 26).

In conclusion, elevated Post-CA 19-9 level was associated with a poor prognosis and predicted by positive surgical margin and Pre-CA19-9 level ≥ 400 U/ml in patients with PDAC who received macroscopically curative resection. Elevated Post-CA 19-9 level was shown to imply a locoregional residual tumor and occult distant metastasis. Although the study results need to be verified by large-sample, multicentric, and prospective studies, predicted or existing elevated Post-CA 19-9 levels could be an adequate indication for the development of novel and alternative treatment strategies for the treatment of patients with PDAC.

Conflicts of Interest

The Authors declare no conflicts of interests for the present article.

Authors' Contributions

C.T. designed the study, collected and analyzed the data, and wrote the manuscript. Y.K., H.S., S.H., M.T., I.O., S.H., and Y.O. interpreted the data and reviewed the manuscript.

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