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ORIGINAL SCIENTIFIC REPORT (INCLUDING PAPERS PRESENTED AT SURGICAL CONFERENCES)

Sustained Elevation of Postoperative Serum Level of Carbohydrate Antigen 19-9 is High-Risk Stigmata for Primary Hepatic Recurrence in Patients with Curatively Resected Pancreatic Adenocarcinoma

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Abstract

Background Survival after surgery for pancreatic adenocarcinoma (PA) is poor and heterogeneous, even for curative (R0) resection. Serum carbohydrate antigen (CA) 19-9 levels are important prognostic markers for resected PA. However, sustained elevation of CA19-9 in association with the patterns of recurrence has been rarely investigated.

Methods Patients who underwent R0 resection ($n = 539$) were grouped according to postoperative serum CA19-9 levels (Group E: sustained elevation; Group N: no elevation). Clinicopathological factors, patterns of recurrence, and survival were compared between the groups.

Results Group E ($n = 159$) had significantly shorter median overall survival (17.1 vs. 35.4 months, $p < 0.0001$) than Group N ($n = 380$). Postoperative CA19-9 elevation was a significant independent predictor of poor survival in multivariate analysis (hazard ratio 1.98, $p < 0.0001$). The rate of hepatic recurrence in Group E was 2.6-fold higher than in Group N (45% vs. 17%, $p < 0.0001$). Postoperative CA19-9 elevation was a strongest independent predictor of primary hepatic recurrence ($p < 0.0001$) by a multiple regression model. Loco-regional, peritoneal, and other distant recurrence did not differ between the groups. The extent of preoperative CA19-9 elevation was correlated sustained elevation of CA19-9 after surgery ($p < 0.0001$) and primary hepatic recurrence ($p = 0.0019$).

Conclusions Sustained CA19-9 elevation was strong predictor of primary hepatic recurrence and short survival in cases of R0 resection for PA.

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Introduction

In cases of pancreatic adenocarcinoma (PA), long-term survival can only be obtained if the tumor is removed without residual disease (R0 resection). Adjuvant chemotherapy confers a greater survival benefit for R0 patients than it does for patients with microscopic residual disease (R1 patients) [1]. Despite R0 resection, however, the median survival time after surgery for PA is only 2 years [2, 3], perhaps as a result of occult metastases at the time of surgery [4].

Carbohydrate antigen (CA) 19-9 has been used as a biomarker for the prediction of recurrence and survival among patients with resected PA [5–17]. Although the serum CA19-9 value (CA19-9) must be within the normal range after complete clearance of the tumor can be achieved, CA19-9 sometimes shows sustained elevation after surgery [5–17]. Sustained elevation of postoperative CA19-9 after surgery is accompanied by poor prognosis [13].

To address various clinical questions surrounding surgical treatments for PA, we have established a common database of seven high-volume pancreatic surgical centers in Japan (Multicenter Study Group of Pancreatobiliary Surgery: MSG-PBS). In the present collaborative study, we have used this large-scale database to analyze perioperative CA19-9 kinetics in patients with R0-resected PA.

Materials and methods

Eligibility criteria and patient selection

We collected and registered 1451 patients who had undergone R0/1 pancreatic resection between 2001 and 2012. Each of these patients was entered into the MSG-PBS database. To be included in this study, patients were required R0 resection to have both pre- and postoperative CA19-9 values available with a serum bilirubin of $\leq$3.0 mg/dl at the time of CA19-9 measurement, and not to have received neoadjuvant treatment (NAT). Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) or positron emission tomography-computed tomography (PET-CT) was not routinely performed for the patients with surgery before 2009. Most of the patients with surgery after 2009 received EOB-MRI or PET-CT to exclude hepatic metastases before surgery. Of 1451 registered cases, we excluded 37 patients with initially unresectable, 13 patients with anaplastic or undifferentiated carcinoma, 342 patients who received NAT, 71 patients without pre- or postoperative CA19-9 assessments, 143 patients with serum bilirubin of >3.0 mg/dl at the time of CA19-9 measurement, patients with undetectable level of preoperative CA19-9 value ($\leq$2 U/ml), 46 patients with positive peritoneal washing cytology, 60 patients with histologically confirmed non-regional nodal metastasis (M1), and 162 patients with microscopically positive margin (R1) tumor. The remaining 539 eligible cases were then analyzed (Fig. 1). Of the 539 patients, 159 cases showed sustained elevated CA19-9 ($\geq$37 U/ml) after resection (Group E) and 380 cases showed no elevation of CA19-9 (<37 U/ml, Group N).

Study design

CA19-9 values were measured using a radioimmunoassay kit in each institution's laboratories. The recommended upper limit of normal (ULN) for CA19-9 is 37 U/ml. Postoperative normalization of CA19-9 was defined by this cutoff value. All postoperative measurements of CA19-9 were taken within the 2 months following surgery. Patients were followed up with CT and serum CA19-9 values every 3 months for the first 2 years and then every 6 months for years 3–5.

We evaluated the following preoperative factors: age; sex; preoperative biliary drainage (yes or no); preoperative CA19-9 (U/ml); maximal tumor size (mm); location of the tumor (head or body/tail of the pancreas); and resectability, based on NCCN guidelines (resectable or borderline). Further, we evaluated the following postoperative factors: stage (according to the 7th AJCC/UICC TNM classification [18, 19]); nodal involvement (N0 or N1); postoperative CA19-9 level (U/ml); and adjuvant therapy (yes or no). The primary recurrent site was categorized as follows: loco-regional, hepatic, peritoneal, or other distant. Recurrence-free survival time was measured from the time of surgery until the detection of primary recurrence or last follow-up (no recurrence). Overall survival time was measured from the time of surgery until death or last follow-up. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review board of each participating hospital.

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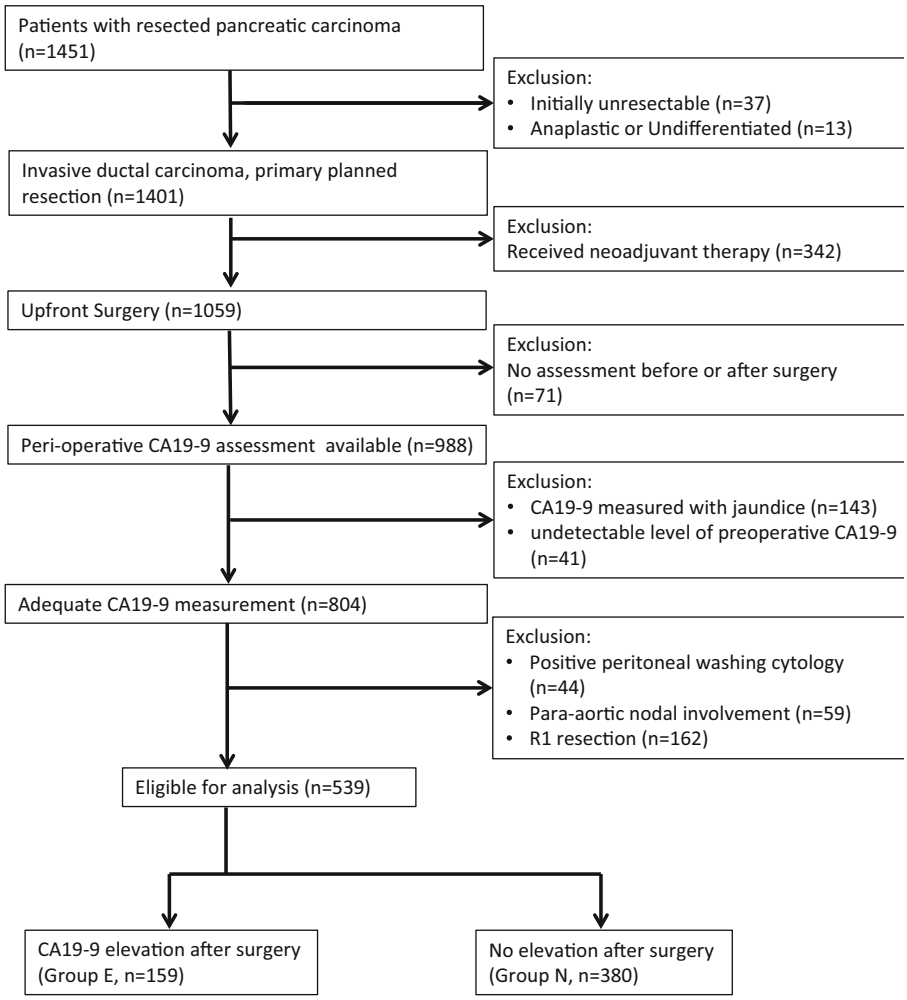

Fig. 1 Schematic flowchart of patient selection and grouping

Statistical analysis

We compared the previously mentioned preoperative and postoperative parameters between the two groups (Group E and Group N). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were expressed as median (range) and compared using the Mann–Whitney *U* test. The median survival time was estimated using the Kaplan–Meier method, and the difference was tested using the log-rank test. A Cox proportional hazards model was fit by including categorized versions of the factors described above. Age was categorized as younger or older, as partitioned by the median age (70 years old). Tumor size was categorized as smaller or larger, as partitioned by the median size (25 mm). A univariate and multivariate logistic regression model was used to examine hepatic recurrence, considering the variables described above.

Statistical analyses were performed using JMP statistical discovery software (JMP version 10.0.2; SAS Institute, Cary, NC, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Baseline demographics and postoperative CA19-9 status

There were no significant differences between Group N and Group E postoperative normalization of CA19-9 in terms of age and gender (Table 1). Preoperative CA19-9 was significantly higher in Group E than it was in Group N ($p < 0.0001$). As compared with the tumors in Group N, tumors were significantly larger in Group E ($p = 0.0049$) and were also more likely to be located in the body or tail of the pancreas ($p < 0.0001$). Considering postoperative characteristics, the frequency of nodal metastasis did not differ significantly between the groups, and most cases (90%) were stage II cases in both groups. The proportion of

Table 1 Descriptive statistics for patients with R0 resection stratified by postoperative normal (Group N) or elevated (Group E) CA19-9 grouping

Characteristics	Group E	Group N	*p*
Number	159	380	
Age (median, year old)	70 (31–86)	69 (32–91)	0.29
≥70; *n* (%)	85 (53)	188 (49)	0.39
Gender; male; *n* (%)	94 (59)	207 (54)	0.32
Biliary drainage; yes; *n* (%)	39 (25)	126 (33)	0.047
Preoperative CA19-9 (median, U/ml)	463.5 (5.9–40,334)	63.8 (2.9–15,231)	<0.0001
Tumor size (median, mm)	28 (0–80)	25 (0–86)	0.0049
>25; *n* (%)	104 (65)	194 (51)	0.0022
Location; head; *n* (%)	78 (49)	264 (69)	<0.0001
Resectability; resectable; *n* (%)	119 (75)	311 (82)	0.069
Stage (TNM)			0.38
I; *n* (%)	14 (8.8)	43 (11)	
II; *n* (%)	145 (91)	337 (89)	
Nodal metastases; N1; *n* (%)	95 (60)	229 (60)	0.91
Postoperative CA19-9 (median, U/ml)	88.7 (37–8943)	13 (0–36.9)	<0.0001
Adjuvant therapy; yes; *n* (%)	139 (87)	314 (83)	0.16

patients receiving adjuvant therapy did not differ significantly between the groups and was over 80% in both groups.

Survival analysis

The overall median survival among all the 539 patients was 29.8 months. The postoperative sustained elevation of CA19-9 (Group E) was associated with poorer survival than postoperative normalized CA19-9 (Group N) (median 17.1 vs. 35.4 months, $p < 0.0001$). Overall 1-, 3-, and 5-year survival rates were 65.7, 24.9, and 17.9% in Group E, and 85.3, 49.4, and 35.4% in Group N, respectively (Fig. 2a). Recurrence-free survival was also significantly shorter in Group E than it was in Group N (median 8.6 vs. 22.6 months, $p < 0.0001$). Recurrence-free 1-, 2-, and 3-year survival rates were 64.6, 18.7, and 11.7% in Group E, and 83.7, 42.9, and 27.0% in Group N, respectively (Fig. 2b).

Univariate analyses were undertaken to determine the variables that were most predictive of survival (Table 2). Older age ($p = 0.018$), head tumor ($p = 0.0049$), borderline tumor ($p < 0.0001$), preoperative CA19-9 elevation ($p < 0.0001$), large tumor ($p < 0.0001$), nodal metastases ($p < 0.0001$), postoperative CA19-9 elevation ($p < 0.0001$), and no adjuvant therapy ($p = 0.0099$) were significantly predictive of poor survival in the univariate analyses. In multivariate analysis, the statistically significant predictors of poor survival were older age (hazard ratio [HR] 1.35, $p = 0.011$), head tumor (HR 1.33, $p = 0.024$), borderline tumor (HR 1.43, $p = 0.013$), large tumor (HR 1.40, $p = 0.0089$), nodal metastases (HR 1.85, $p < 0.0001$), postoperative CA19-9 elevation (HR 1.98, $p < 0.0001$), and no adjuvant therapy (HR 1.57, $p = 0.0044$).

Patterns of recurrence

The overall recurrence rate was significantly higher in Group E than it was in Group N (85 vs. 61%, $p < 0.0001$). The patterns of primary recurrent sites were compared between the groups. Primary hepatic recurrence was 2.6 times more common in Group E as it was in Group N (45 vs. 17%, $p < 0.0001$). However, the frequencies of primary loco-regional ($p = 0.50$), peritoneal ($p = 0.63$), and other distant recurrence ($p = 0.64$) did not differ between the groups (Fig. 3). In Group E, 24 patients (15%) did not develop recurrence at the time of analysis. The patients without recurrence had significant smaller tumor ($p = 0.0067$), lesser nodal metastases ($p = 0.0010$), and lower extent of postoperative CA19-9 elevation ($p < 0.0001$) than those with recurrence.

A logistic regression model was used to examine primary hepatic recurrence (Table 3). By multivariate regression analysis, postoperative elevation of CA19-9 (HR 4.05, $p < 0.0001$), large tumor (HR 1.86, $p = 0.0080$), and nodal metastases (HR 1.76, $p = 0.015$) were statistically significant independent predictors of primary hepatic recurrence. Postoperative elevation of CA19-9 elevation was the most significant predictor.

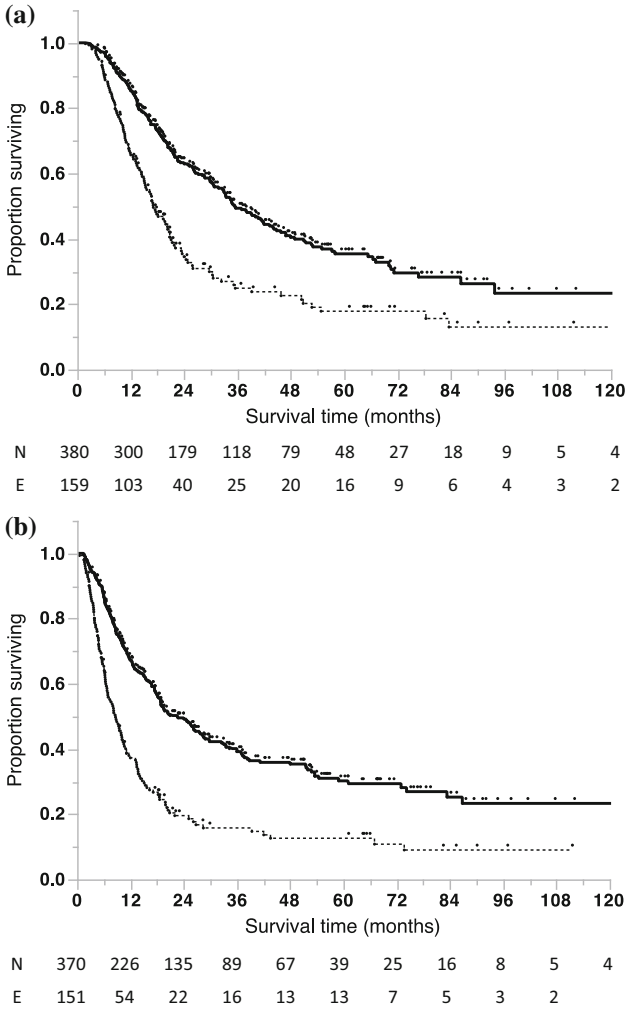

Fig. 2 Kaplan–Meier survival cumulative curves for patients with R0 resection stratified by postoperative normal (Group N) or elevated (Group E) CA19-9 grouping denoting overall (**a**) and recurrence-free (**b**) survival. The numbers at patients at risk of each time interval are provided below

The influence of the extent of preoperative CA19-9 elevation was evaluated on the sustained elevation of postoperative CA19-9 elevation and primary hepatic recurrence (Fig. 4). There was a significant correlation between the extent of preoperative CA19-9 elevation and the proportion of postoperative CA19-9 elevation ($p < 0.0001$). The proportion of primary hepatic recurrence was significantly increased depending on the extent of preoperative CA19-9 ($p = 0.0019$). The extent of postoperative CA19-9 elevation had a significant correlation with the proportion of primary hepatic recurrence ($p < 0.0001$) and recurrence-free survival ($p < 0.0001$, Supplemental Figure).

Discussion

Early recurrence of distant organ metastases occurs frequently, even after R0 resection for PA, suggesting that the onset of these metastases might predate surgery [13, 15]. Patient survival after surgery is not homogenous; to date, prognostic algorithms have been unable to predict patient survival after surgery for PA in a reliable manner. In an attempt to improve predictions of patient outcomes, we analyzed the utility of postoperative sustained elevation of CA19-9 to predict the survival for the patient only with curative resection. Although preoperative CA19-9 elevation has been reported to be predictors of poor survival, multivariate analyses revealed that postoperative CA 19-9 level, not preoperative CA 19-9 level, was an independent prognostic factor (Table 2) associated with primary hepatic recurrence (Table 3). Preoperatvie and postoperative CA19-9 elevations are significantly correlated, and the influence of preoperative CA19-9 elevation on survival was canceled at least partially by postoperative CA19-9 elevation (Fig. 4). The novelty of this study lied in the

Table 2 Univariate and multivariate Cox proportional hazard model analyses for overall survival

Factors		Univariate		Multivariate	
		Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age	≥70 year old	1.31 (1.05–1.64)	0.018	1.35 (1.08–1.70)	0.011
Gender	Male	1.04 (0.84–1.31)	0.69	1.02 (0.82–1.29)	0.84
Location	Head	1.40 (1.11–1.78)	0.0049	1.33 (1.04–1.72)	0.024
Resectability	Borderline	1.99 (1.53–2.55)	<0.0001	1.43 (1.08–1.88)	0.013
Preoperative CA19-9	Elevation (≥37 U/mL)	1.74 (1.32–2.32)	<0.0001	1.05 (0.77–1.44)	0.77
Tumor size	≥25 mm	1.83 (1.46–2.32)	<0.0001	1.40 (1.09–1.81)	0.0089
Nodal metastases	Positive	2.14 (1.68–2.73)	<0.0001	1.85 (1.44–2.40)	<0.0001
Postoperative CA19-9	Elevation (≥37 U/mL)	1.95 (1.54–2.45)	<0.0001	1.98 (1.53–2.55)	<0.0001
Adjuvant therapy	No	1.48 (1.10–1.96)	0.0099	1.57 (1.16–2.09)	0.0044

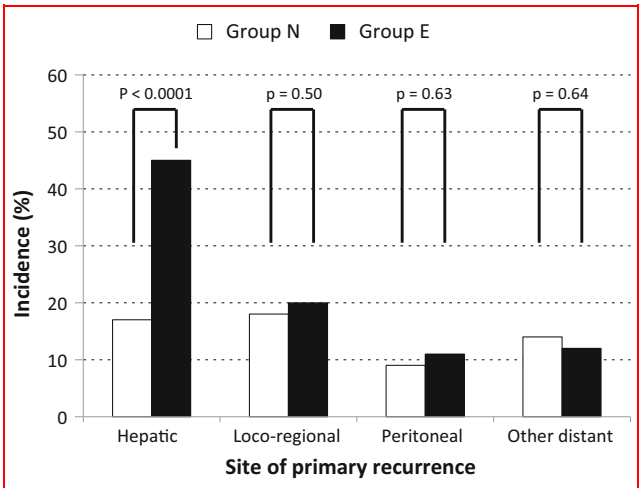

Fig. 3 Comparison of the incidence of primary recurrence site between postoperative normalized (Group N) or elevated (Group E) CA19-9 grouping

demonstration of sustained elevation of CA19-9 as a high-risk predictor for hepatic recurrence for the patients after complete local clearance. The previous literature [12–14, 17] includes retrospective studies, as well as a prospective analysis by Berger et al. [8], which demonstrated the prognostic importance of the CA19-9 levels after surgery with curative intent. In their multivariate analysis, the authors found that the independent predictors of survival were CA19-9 level and nodal involvement. Although all previous studies included R1 resection, similar predictors of survival were shown for the patients with R0 resection (Table 2). Analyzing the largest cohort for R0 resected PA, our results further confirm the importance of CA19-9, nodal metastasis, and adjuvant therapy [1–3] as predictors of survival [5, 6, 8, 13–15, 17].

We investigated associations between sustained elevation of CA19-9 and the site of primary recurrence. We observed that primary hepatic recurrence was 2.6 times more common among patients with sustained elevation of CA19-9 as it was among patients with normalized CA19-9, despite the similarity of the other site recurrence rate in both groups (Fig. 3). Our multivariate logistic regression model also revealed that the sustained elevation of CA19-9 was a strongest and independent predictor of hepatic recurrence (Table 3). This result strongly suggests that the sustained CA19-9 elevation after surgery was mainly produced by hepatic micro-metastases that were undetectable at the time of surgery [13, 17]. This hypothesis was also supported by the significant negative impact of postoperative sustained elevation of CA19-9 on survival (Fig. 2). In a large single-institution series, Hartwig et al. [20] showed that high serum preoperative CA19-9 levels were among the strongest predictors of poor survival, although their investigation did not clarify whether high serum CA19-9 reflected tumor burden or aggressiveness. In the present study, postoperative elevated CA19-9 after complete local clearance, not preoperative elevation of CA19-9, was closely associated with a high rate of hepatic recurrence (Table 3). This observation suggests that some of the patients with high serum CA19-9 may have had hepatic micro-metastases that predated the resection of pancreatic cancer, resulting in poorer survival. However, other factors related to the production, secretion, and metabolism of CA19-9 may certainly have contributed to the elevated values observed in this study [21].

In this study, the patients received NAT were excluded. Because NAT can decrease CA19-9 [22–26], further analyses are necessary to determine whether the normalization of CA19-9 by NAT has an impact on prognosis or patterns of recurrence. High level of pretreatment CA19-9 levels, which were closely associated with hepatic relapse (Fig. 4), may be candidate for systemic treatment before surgery. As shown in Table 2, adjuvant therapy had little impact for the development of primary hepatic recurrence. Taking into the consideration that Group E showed short survival (Fig. 2) although more than 80% of the patients received adjuvant therapy in Group E (Table 1), more effective adjuvant is needed to improve outcome. Albumin-

Table 3 Univariate and multivariate logistic regression model for primary hepatic recurrence

Factors		Univariate		Multivariate	
		Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age	≥70 year old	1.01 (0.68–1.50)	0.96	1.08 (0.70–1.67)	0.72
Gender	Male	1.34 (0.90–2.01)	0.16	1.25 (0.81–1.93)	0.32
Location	Head	1.04 (0.69–1.58)	0.86	1.28 (0.80–2.05)	0.30
Resectability	Borderline	1.42 (0.88–2.27)	0.15	1.07 (0.49–1.25)	0.80
Preoperative CA19-9	Elevation (≥37 U/mL)	1.90 (1.17–3.19)	0.0090	1.17 (0.66–2.09)	0.59
Tumor size	≥25 mm	2.25 (1.49–3.45)	0.0001	1.86 (1.17–2.95)	0.0088
Nodal metastases	Positive	1.87 (1.23–2.88)	0.0032	1.76 (1.11–2.79)	0.016
Postoperative CA19-9	Elevation (≥37 U/mL)	3.80 (2.50–5.80)	<0.0001	4.05 (2.49–6.57)	<0.0001
Adjuvant therapy	No	1.19 (0.69–2.15)	0.54	1.09 (0.59–2.03)	0.78

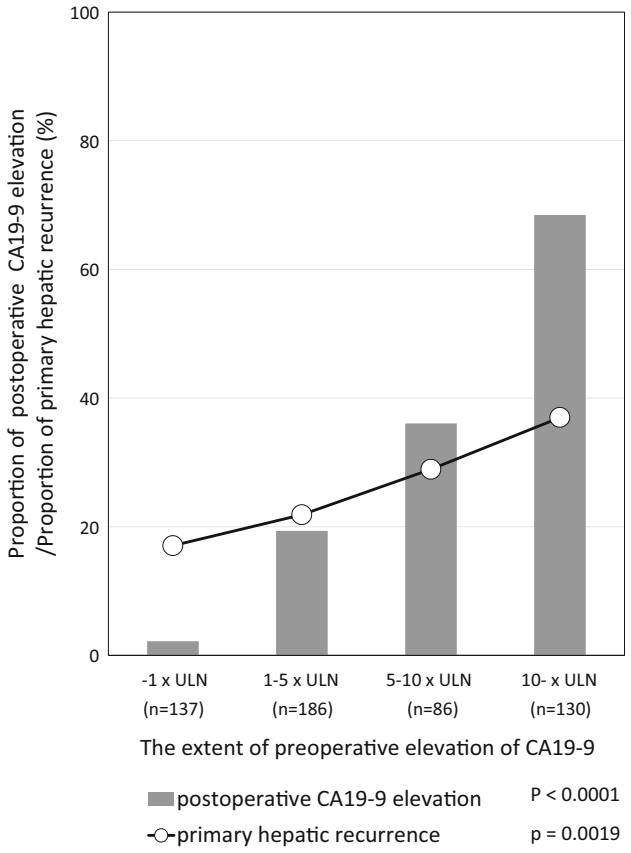

Fig. 4 Proportion of postoperative sustained elevation of CA19-9 and primary hepatic recurrence between the groups stratified preoperative CA19-9 value. The gray bar indicated the proportion of the cases with postoperative elevation of CA19-9 in each group. The line indicated the proportion of the cases with primary hepatic recurrence in each groups. ULN indicated upper limit of normal (37 U/ml) CA19-9 values

bound paclitaxel (nab-paclitaxel) plus gemcitabine increased the survival for the patients with metastatic pancreatic carcinoma [27]. Further studies are necessary to test whether this powerful treatment as adjuvant or as NAT is useful for preventing hepatic recurrence.

As a retrospective study, the present investigation was naturally subject to limitations, confounding factors, and selection biases. Notably, the patients for whom CA19-9 measurements were available may have had somewhat different prognoses than the patients for whom CA19-9 measurements were unavailable; any substantial difference would constitute a selection bias. However, we found no significant differences between the eligible and total cohorts in terms of stage or survival. Another issue is posed by the study design for the database, which spans 2001–2012. Recent advances have resulted in better diagnostic methods and treatment outcomes for PA and may also affect CA19-9 kinetics. Although the present study was limited by its retrospective design, we found evidence that postoperative CA19-9 remained significantly and negatively associated with survival after controlling for known prognostic factors in multivariate analysis.

In conclusion, the normal value of CA19-9 after resection had a significant prognostic impact for patients with R0-resected PA. Failure to normalize was associated with frequent hepatic relapse and shorter survival. Among patients who had high preoperative CA19-9, the postoperative sustained elevation of CA19-9 was common, and prognoses were poor. These patients should be considered for alternative strategies, including NAT and effective adjuvant therapy.

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Compliance with ethical standards

Conflicts of interest The authors have no potential conflicts of interest to disclose.

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