



Diagnostic impact of postoperative CA19-9 dynamics on pancreatic cancer recurrence: a single-institution retrospective study

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Abstract

Postoperative CA19-9 elevation after pancreatic cancer resection suggests recurrence but can also occur in benign conditions. This study aimed to investigate the interpretation of postoperative CA19-9 elevation after pancreatic cancer surgery in terms of cancer recurrence. A cohort of patients undergoing pancreatectomy for pancreatic cancer at our hospital was included. Among them, 52 patients exhibited postoperative CA19-9 elevation without radiological evidence of recurrence. These patients were evaluated with follow-up CA19-9 measurements. The CA19-9 increase rates were calculated based on the first elevation and the follow-up measurement. The association between the CA19-9 increase rate and tumor recurrence was assessed. Patients with a CA19-9 increase rate of $\geq 30\%$ had a significantly higher frequency of recurrence within 3 months compared to those without such an increase ($p=0.0002$). Multivariate analysis demonstrated that a CA19-9 increase rate of $\geq 30\%$ was an independent risk factor for recurrence (odds ratio 8.17, $p=0.0309$). The CA19-9 value at the first elevation ($p=0.1794$) and at the follow-up measurement ($p=0.1121$) were not associated with recurrence. After the first postoperative CA19-9 elevation, the CA19-9 increase rate based on follow-up measurements can serve as a predictive factor for tumor recurrence.

Keywords CA19-9 · Pancreatic cancer · Recurrence · Dynamics · Postoperative follow-up

Introduction

In the postoperative setting following curative resection for pancreatic cancer, the current guidelines recommend regular follow-up at an interval of 3–6 months because an intense follow-up has not been found to impact patients' survival rates [1]. However, a recent study has indicated that early detection of tumor recurrence could potentially prolong survival due to advancements in chemotherapy [2]. In this context, several approaches have been explored to identify recurrence at an early stage, with particular attention being drawn to carbohydrate antigen 19-9 (CA19-9) [3].

Although a postoperative elevation of CA19-9 is associated with cancer recurrence, a postoperative elevation of CA19-9 often precedes radiological confirmation of

recurrence [4]. Moreover, elevated CA19-9 can also be attributable to benign causes, such as postoperative cholangitis [5] or exacerbated diabetes mellites [6]. Therefore, when a patient shows an elevated postoperative CA19-9 level, the clinical impact of the elevation can be further evaluated by obtaining a follow-up CA19-9 measurement. A markedly increased CA19-9 level at follow-up may indicate that tumor recurrence is likely, while a follow-up level within the normal range might suggest that the CA19-9 elevation was attributable to other causes. There remains a need to further study the impact of the dynamics of postoperative CA19-9 levels, to determine how to optimize the use of this marker to stratify patients according to risk of recurrence.

In the current study, we identified patients who underwent pancreatectomy for pancreatic cancer, exhibited elevated postoperative CA19-9 without radiographic recurrence, and then underwent follow-up measurement of CA19-9. Within this patient group, we calculated the rate of CA19-9 change between the first elevated measurement and the follow-up measurement, and we evaluated the significance of CA19-9 dynamics in association with the risk of tumor recurrence.

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Methods

Patient selection

The current study was performed in compliance with the Declaration of Helsinki, and was approved by the ethical committee of our hospital (approval number 22507). CA19-9 was consistently measured in our institution, and an elevated CA19-9 level was defined as over 37 U/mL. With the aim to exclude CA19-9 elevations caused by non-cancerous events such as cholangitis, cases were excluded in which CA19-9 elevation (i.e., > 37 U/mL) accompanies a simultaneous elevation of total bilirubin level of > 3.0 mg/dL. We retrospectively reviewed the cases of 310 consecutive patients who underwent pancreatectomy for pancreatic cancer at our hospital between 2010 and 2020. Pre- and postoperative CA19-9 measurements were retrieved. Figure 1 shows the diagram of patient enrollment. Among the 310 patients reviewed, 50 were excluded from the analysis (Fig. 1, Exclusion criteria #1) for the following reasons: 21 patients did not achieve complete tumor resection due to intraoperatively diagnosed distant metastasis or local invasion, 16 were not followed-up at our hospital, and 13 showed a persistently undetectable CA19-9 level (i.e., Lewis negative population [7]). Among the remaining 260 patients, 137 were excluded (Exclusion criteria #2) because CA19-9 did not normalize within 2 months from surgery ($n=72$), or postoperative CA19-9 measurements were persistently within the normal range ($n=65$). After these exclusions, 123 patients were identified, whose CA19-9 level normalized within 2 months

from surgery, and then increased to an abnormal level (> 37 U/mL; defined as the first elevation). Among these patients, 85 were subject to a follow-up CA19-9 measurement within 2 months after the first elevation (Exclusion criteria #3). For these 85 patients, we calculated the CA19-9 increase rate between the first elevation and follow-up measurement, and evaluated the association between this rate and future tumor recurrence. All of the patients included in this analysis underwent routine follow-ups for at least 2 years after surgery.

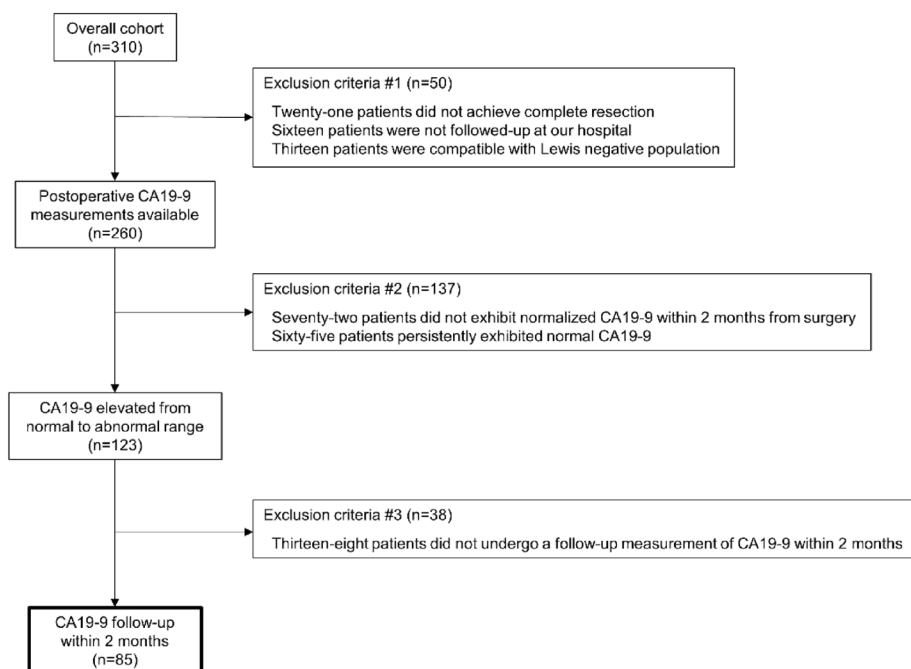
CA19-9 increase rate (%)

$$= \frac{\text{CA19-9 at follow up measurement} - \text{CA19-9 at first elevation}}{\text{CA19-9 at first elevation}} \times 100$$

Postoperative management and diagnosis of recurrence

The postoperative surveillance of CA19-9 was started before the initiation of adjuvant chemotherapy. Adjuvant chemotherapy was administered using either S-1 or gemcitabine, depending on the patient's overall health status. Regular monitoring, using laboratory testing or CT scans, was performed at an interval of every 1–3 months regardless of the presence or absence of symptoms suggestive of tumor recurrence. Tumor recurrence was defined as the reappearance of a malignant growth, confirmed by histological or radiological examinations. Radiological assessments included CT scans, magnetic resonance imaging (MRI),

Fig. 1 Scheme of patient enrollment. Exclusion criteria #1 ($n=50$) included patients who did not undergo surgery with curative intent ($n=21$), who were not followed-up at our hospital ($n=16$), and who persistently exhibited an undetectable CA19-9 level (i.e., Lewis negative population; $n=13$). Exclusion criteria #2 ($n=137$) included patients whose CA19-9 level did not normalize within 2 months from surgery ($n=72$), and whose CA19-9 level was persistently within the normal range throughout the surveyed period ($n=65$). Exclusion criteria #3 included patients who did not undergo a follow-up CA19-9 measurement within 2 months from the first elevation



and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). Moreover, the value of postoperative CA19-9 did not affect the diagnosis of recurrence.

Patient characteristics

We analyzed the relationships between tumor recurrence and the selected patients’ demographic information, including sex, age at the time of surgery, body mass index, preoperative therapy, type of surgical procedure, surgical duration, blood loss, postoperative pancreatic fistula grade [8], histological results [9], postoperative therapy, and postoperative CA19-9 levels. The TNM classification of the tumor was determined based on the 8th edition of Union for International Cancer Control (UICC) TNM classification [10].

Statistical analysis

Patient characteristics were evaluated using chi-square statistics and the Mann–Whitney U test. To determine the optimal cut-off levels of each clinical variable for predicting tumor recurrence, we constructed receiver operating characteristic (ROC) curves (Youden index) in univariate and multivariate analyses. Variables with $p < 0.05$ were incorporated into a logistic regression model to determine independent risk factors for tumor recurrence, which were described with odds ratios. Statistical significance was defined as $p < 0.05$ derived from two-tailed tests. All statistical analyses were performed using JMP software (JMP, version 13.2.1).

Results

Association between the dynamics of CA19-9 and tumor recurrence

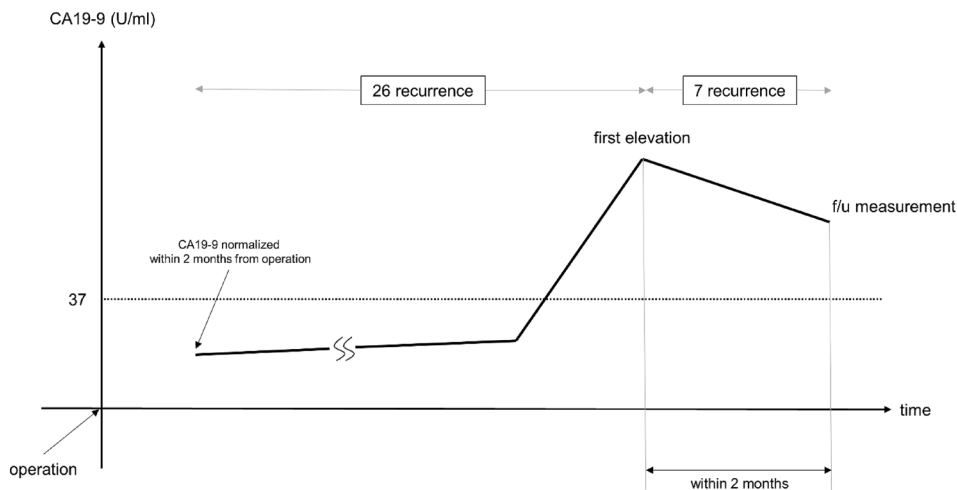
The data obtained from the entire cohort ($n = 85$) regarding patient characteristics, recurrence free survival (RFS) were presented in Supplementary Fig. 1, and Supplementary Table 1.

The dynamics of postoperative CA19-9 were evaluated in association with tumor recurrence, among the 85 patients whose CA19-9 level normalized after surgery and then increased to an abnormal level, and for whom a follow-up measurement was available within a 2-month interval (Fig. 1). The results are summarized in Fig. 2, which shows that 26 patients developed tumor recurrence before the first elevation of CA19-9, 7 patients developed recurrence between the first elevation and the follow-up measurement of CA19-9, while 52 patients had not developed recurrence at the time of the follow-up measurement.

Predictive value of CA19-9 increase rate for tumor recurrence

The 52 patients, who had not yet experienced tumor recurrence at the time of the follow-up measurement, were assessed for subsequent recurrence. The gap between surgery and the first measurement of postoperative CA19-9, and the gap between surgery and the first postoperative CT imaging were 44 ± 24.2 and 100.5 ± 36.7 days (median \pm SD), respectively. Moreover, the intervals of CA19-9 measurement and CT imaging were 42.5 ± 18.0 , and 92 ± 31.8 days (median \pm SD), respectively. Next, we calculated the CA19-9 increase rate between the first elevation and follow-up. We further evaluated whether this rate could be used to predict

Fig. 2 Dynamics of postoperative CA19-9 and tumor recurrence. Patients who exhibited an elevated CA19-9 level (first elevation) were subject to a follow-up measurement. Tumor recurrence was observed prior to the first elevation in 26 patients, whereas recurrence occurred between the first elevation and the follow-up measurement in 7 patients. *f/u* follow-up



recurrence within 3 months after the follow-up measurement. As shown in Fig. 3a, an elevated level of CA19-9 increase rate was associated with a higher frequency of tumor recurrence. In Fig. 3b, a ROC curve shows the association between the CA19-9 increase rate and tumor recurrence. We determined that a 30% rate of CA19-9 increase was an optimal cut-off value, which yielded 73.9% sensitivity and 79.3% specificity in predicting tumor recurrence within 3 months from the follow-up measurement.

Assessment of tumor recurrence risk based on the CA19-9 increase rate

Based on the ROC curve, the 52 patients were classified into three groups according to the CA19-9 increase rate (Fig. 4a). Type A patients exhibited a CA19-9 increase rate of over 30% at the follow-up measurement ($n=23$); Type B patients exhibited an abnormal CA19-9 value at the follow-up measurement (>37 U/mL), but the increase rate was $\leq 30\%$ ($n=16$); and Type C patients exhibited a normalized CA19-9 level at the follow-up measurement ($n=13$). As presented in Fig. 5, the 3-year RFS in patients of Types A, B, and C was 8.7%, 18.8%, 46.2%, respectively, with a statistical difference between Types A and C ($p=0.0073$). The recurrence rate according to the 3 Types was summarized in Fig. 4b. Among the 23 Type A patients, 17 (73.9%) experienced recurrence within 3 months from the follow-up measurement. On the

other hand, recurrence within 3 months occurred in 5 of 16 Type B patients (31.3%), and 1 of 13 Type C patients (7.7%). The recurrence rates did not significantly differ between the Type B and Type C groups ($p=0.1834$). In contrast, the recurrence rate in the Type A group was significantly higher than in the Type B ($p=0.0112$) and Type C ($p=0.0003$) groups.

Therefore, the 52 patients were divided into two groups according to recurrence risk. The high-risk group included the Type A patients, in which 73.9% (17/23) of patients experienced recurrence. The low-risk group included the Type B and C patients, in which 20.7% (6/29) of patients experienced recurrence. The recurrence rate was significantly higher in the high-risk group compared to the low-risk group ($p=0.0002$).

Patients' characteristics according to the risk of tumor recurrence

Table 1 summarizes the patients' characteristics based on their risk of tumor recurrence. Compared to patients in the low-risk group, patients in the high-risk group were significantly younger ($p=0.0483$) and had a significantly higher proportion of well-differentiated carcinoma ($p=0.0493$). Additionally, patients in the high-risk group underwent adjuvant chemotherapy at a significantly higher rate than patients in the low-risk group ($p=0.0283$).

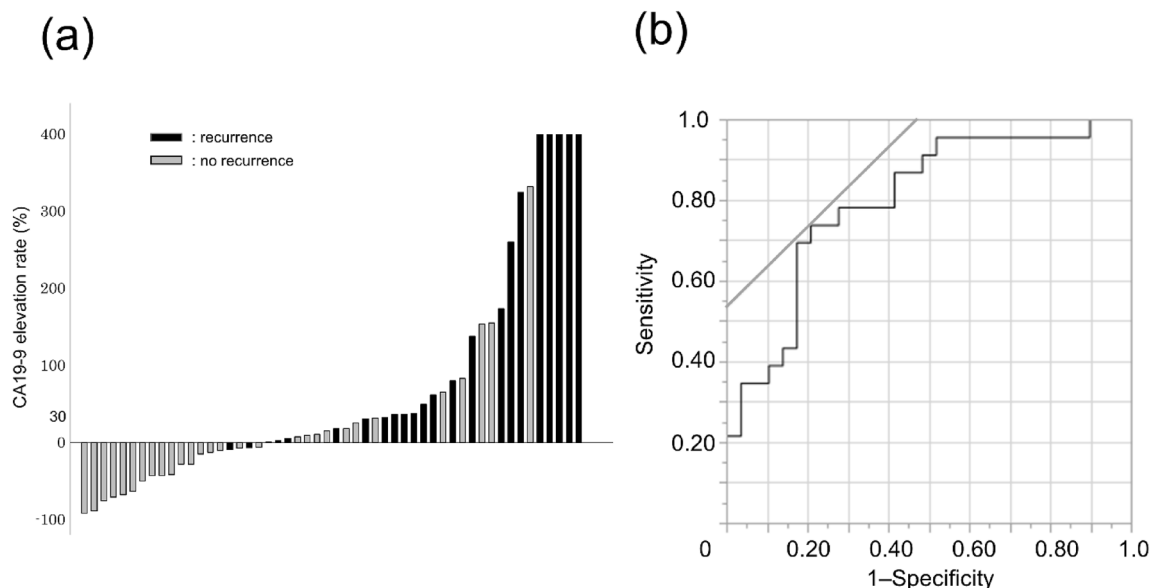


Fig. 3 Association between the CA19-9 increase rate and tumor recurrence. **a** Each patient's CA19-9 increase rate relative to tumor recurrence. An elevated CA19-9 increase rate was associated with tumor recurrence. **b** ROC curve showing the association between CA19-9 increase rate and tumor recurrence. The CA19-9 increase

rate showed moderate accuracy for predicting tumor recurrence within 2 months after the follow-up measurement (AUC: 0.80). The optimal cut-off value for the CA19-9 increase rate was calculated to be 30% (Youden index), which predicted tumor recurrence with 73.9% sensitivity and 79.3% specificity

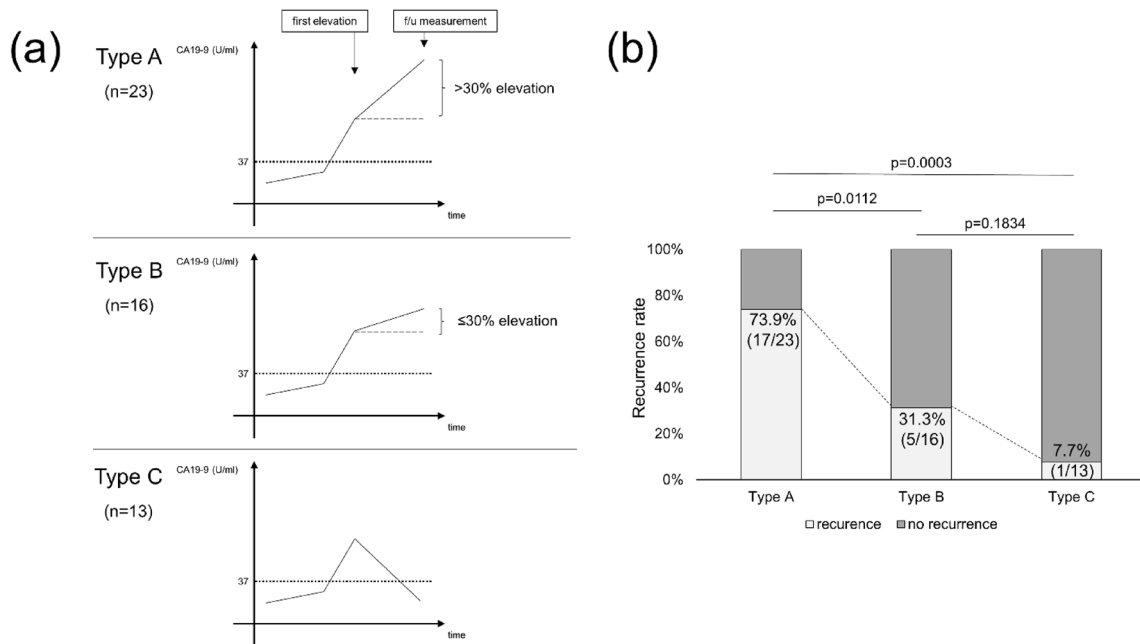


Fig. 4 Classification of the dynamics of CA19-9 and recurrence risk. **a** The dynamics of CA19-9 was categorized into three types based on the cut-off of 30% obtained from the ROC curve. Type A patients exhibited an >30% increase at the follow-up measurement. Type B patients had an abnormal follow-up measurement, but an increase of ≤30%. Type C patients had a normalized follow-up measurement. **b** The recurrence rate within 3 months after the follow-up measure-

ment is shown according to the three types. Recurrence occurred in 73.0% of Type A patients, which was significantly higher than the recurrence rates among Type B patients ($p=0.012$) and Type C patients ($p=0.003$). Recurrence occurred in 31.3% of Type B patients, and in 7.7% of Type C patients, and these rates did not significantly differ ($p=0.0184$). *f/u* follow-up

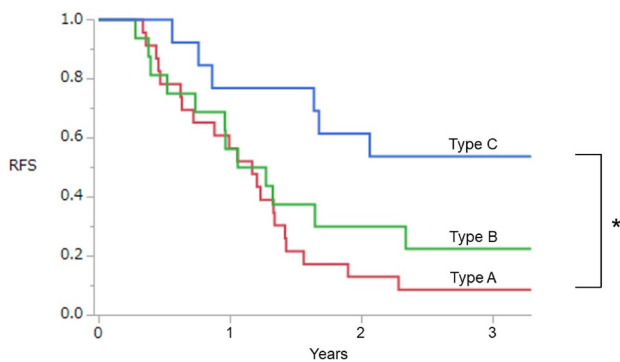


Fig. 5 Recurrence free survival in Types A, B, and C. The 3-year RFS was 8.7% in Type A, 18.8% in Type B, and 46.2% in Type C, respectively, with a significant difference between Types A and C ($p=0.0073$). *RFS* recurrence free survival

Univariate and multivariate analysis to identify risk factors for tumor recurrence

Table 2 displays the clinical variables that were assessed in association with tumor recurrence within 3 months from the follow-up measurement, using both univariate and multivariate logistic regression models. Univariate analysis revealed four factors that were significantly associated with tumor

recurrence: age > 61 years, CA19-9 of > 50 U/mL at the first elevation, CA19-9 of > 77 U/mL at the follow-up measurement, and categorization in the high-risk group. However, in multivariate analysis, only classification in the high-risk group was identified as an independent risk factor for tumor recurrence within 3 months (OR 8.1706, $p=0.0309$). Supplementarily, the risk factors for tumor recurrence before the elevation of CA19-9 were assessed in the univariate and multivariate analysis (Supplementary Table 2).

Discussion

The management of patients who exhibit a postoperative elevation of CA19-9 is complicated by recent evidence showing that CA19-9 elevation precedes the radiological appearance of tumor recurrence by 6–18 months [4]. In our current study, the first elevation of CA19-9 preceded radiological confirmation of recurrence by a median of 91 days (IQR: 42-297) in the entire cohort. Moreover, in the patients who experienced recurrence before the first elevation of CA19-9, the median of an interval between the radiological confirmation and the CA19-9 elevation was 158 days (IQR: 17-381). Since CA19-9 elevation may imply future tumor recurrence, its predictive value must be validated. Here we evaluated

Table 1 Patient's characteristics

	High-risk group (n = 23)	Low-risk group (n = 29)	p value
Age (years old) (median, range)	71 (41–86)	73 (54–84)	0.0483
Sex (male)	16 (69.57%)	19 (65.52%)	> 0.9999
BMI (kg/m ²) (median, range)	21.6 (16.3–29.0)	22.3 (16.2–30.0)	0.6503
cT* (> 2)	2 (8.70%)	5 (17.24%)	0.4437
cN* (> 0)	3 (13.04%)	3 (0%)	0.0801
Neoadjuvant therapy	17 (73.91%)	23 (79.31%)	0.7455
Preoperative CA19-9 (U/mL) (median, range)	56 (10–634)	43 (7–839)	0.3837
Procedure (Pancreaticoduodenectomy)	14 (60.87%)	15 (51.72%)	0.5811
Operative time (min) (median, range)	445 (213–828)	389 (211–639)	0.3911
Intraoperative bleeding (mL) (median, range)	460 (0–6120)	480 (50–2730)	0.2093
R0 resection	21 (91.30%)	28 (96.55%)	0.5775
Histology (well differentiated adenocarcinoma)	17 (73.91%)	13 (44.83%)	0.0493
pT* (> 2)	4 (17.39%)	6 (20.69%)	> 0.9999
pN* (> 0)	14 (60.87%)	12 (41.38%)	0.2640
Adjuvant chemotherapy	23 (100%)	23 (79.31%)	0.0283
POPF (grade B/C)	5 (21.74%)	5 (17.24%)	0.7341
CA19-9 at first elevation (U/mL) (median, range)	65 (39–2474)	46 (37.5–493)	0.1794
CA19-9 at f/u measurement (U/mL) (median, range)	180 (51–19,374)	40 (11–121)	0.1121

BMI, body mass index; POPF, postoperative pancreatic fistula; CA19-9, carbohydrate 19-9; f/u, follow-up

*TNM classification of the tumor was based on the 8th Edition of the UICC TNM classification

the impact of elevated CA19-9 by calculating the CA19-9 increase rate between the first elevation and a follow-up measurement.

Our multivariate analysis results clearly demonstrated the importance of the CA19-9 increase rate, revealing that tumor recurrence was significantly associated with the CA19-9 increase rate ($p = 0.0309$), but not with the CA19-9 value itself at the first elevation or at the follow-up measurement (Table 2). The predictive value of the CA19-9 increase rate was previously evaluated by Azizian et al., who reported that a single elevation of CA19-9, if it increased by over 2.45-fold, was associated with tumor recurrence with 45% sensitivity and 85% specificity [11]. They proposed that this cut-off might be useful in the selection of patients who would benefit from “CA19-9-orientated” chemotherapy for subclinical recurrence; however, the low sensitivity raises the concern that 45% of patients with subclinical recurrence may be overlooked. In our current study, the CA19-9 increase rate was calculated using the values of the first elevation and the follow-up measurement, and predicated tumor recurrence with 73.9% sensitivity and 79.3% specificity. Together, these results suggest that, although a single CA19-9 elevation can identify patients at risk of subclinical recurrence, the CA19-9 increase rate based on a follow-up measurement can predict subclinical recurrence with greater sensitivity. However, further studies are needed to validate this hypothesis.

In our current study, the Type B group included patients whose CA19-9 level at follow-up showed neither a marked increase nor normalization (Fig. 4). The management of this patient group presents a clinical challenge because an interpretation of this “mildly elevated CA19-9” has never been discussed. Although our analysis revealed that the recurrence risk did not significantly differ between the Type B and Type C groups ($p = 0.1834$; Fig. 4), this result may have been due to the small number of cases surveyed in this study. Notably, the recurrence rate decreased in the order of Types A, B, and C (Fig. 4). Therefore, the Type B patients may require closer postoperative follow-up than the Type C patients.

Intense postoperative follow-up is not currently recommended for pancreatic cancer patients because it does not improve survival [12]. On the contrary, in other cancers such as colorectal cancer, postoperative follow-up modified according to the recurrence risk is recommended [13]. Therefore, in pancreatic cancer patients, stratification of recurrence risk would be desired if it could improve patients' survival. Based on our findings that recurrence risk can be stratified by the CA19-9 increase rate, we propose the following strategy as for patient management according to the dynamics of CA19-9. Type A patients, of whom 73.9% experienced recurrence, may warrant further evaluation for subclinical recurrence using other methods, such as ctDNA analysis [14]. Type B patients, of whom 31.3% experienced recurrence, may require close

Table 2 Univariate and multivariate analysis for tumor recurrence

	n/n	Univariate			Multivariate		
		OR	95% CI	p value	OR	95% CI	p value
Age (> 61 vs. ≤ 61 years)	15/8	0.2163	0.0497–0.9421	0.0439	0.3464	0.0608–1.9749	0.2326
Sex (male vs. female)	15/8	0.8428	0.2634–2.7026	> 0.9999			
BMI (> 19.1 vs ≤ 19.1 kg/m ²)	17/6	1.0794	0.3134–3.7174	> 0.9999			
cT* (> 2 vs. ≤ 2)	3/20	0.9375	0.1877–4.6821	> 0.9999			
cN* (> 0 vs. 0)	3/0	N/A	N/A	0.0891			
Neoadjuvant therapy (yes vs. no)	20/3	3.0000	0.7064–12.7407	0.1879			
Preoperative CA19-9 (> 37 vs. ≤ 37 U/mL)	14/9	1.0980	0.3594–3.3547	> 0.9999			
Procedure (Pancreaticoduodenectomy vs. others)	15/8	2.0090	0.6519–6.1911	0.2689			
Operative time (> 570 vs. ≤ 570 min)	6/17	3.0588	0.6725–13.9123	0.1610			
Intraoperative bleeding (> 750 vs. ≤ 750 mL)	8/15	2.5600	0.7045–9.3019	0.2014			
R status (1 vs. 0)	1/22	0.6136	0.0521–7.2227	> 0.9999			
Histology (well differentiated adenocarcinoma vs. others)	10/13	0.9176	0.3033–2.7765	0.9176			
pT (≥ 2 vs. < 2)	21/2	4.0000	0.7580–21.1080	0.1552			
pN (> 0 vs. 0)	13/10	1.6000	0.5313–4.8181	0.5771			
L (> 0 vs. 0)	13/4	0.8718	0.2031–3.7417	> 0.9999			
V (> 0 vs. 0)	12/5	1.5000	0.3558–6.3234	0.7166			
Pn (> 0 vs. 0)	6/11	0.6471	0.1657–2.5267	0.7285			
Adjuvant chemotherapy (yes vs. no)	21/2	1.6800	0.2794–10.1005	0.6821			
POPF (grade B/C vs. BL)	4/19	0.8070	0.1983–3.2841	> 0.9999			
CA19-9 at first elevation (> 50 vs. ≤ 50 U/mL)	15/8	3.5625	1.1280–11.2516	0.0495	3.4810	0.7200–16.8296	0.1208
CA19-9 at f/u measurement (> 77 vs. ≤ 77 U/mL)	14/9	7.4667	2.0832–26.7623	0.0016	1.2355	0.1647–9.2693	0.8370
CA19-9 dynamics (High-risk vs. Low-risk group)	17/6	10.8611	2.9789–39.5995	0.0002	8.1706	1.2128–55.0455	0.0309

OR odds ratio, CI confidential interval, BMI body mass index, POPF postoperative pancreatic fistula, BL biochemical leak, CA19-9 carbohydrate 19-9, f/u follow-up

*TNM classification of the tumor was based on the 8th Edition of the UICC TNM classification

follow-up. Finally, Type C patients, of whom 7.7% experienced recurrence, may require routine follow-ups as recommended in the guidelines (e.g., every 3–6 months) [15]. The modification of postoperative management according to the dynamics of CA19-9 may identify patients who will benefit from intense follow-up and those who can be conventionally managed. However, the clinical impact of this strategy must be evaluated in terms of whether it can prolong patients’ survival. Moreover, further studies are needed to investigate how the dynamics of CA19-9 are influenced by neoadjuvant regimen, postoperative cholangitis, and adjuvant chemotherapy.

The present study has several limitations. First, due to its retrospective nature, we must carefully interpret the impact of the CA19-9 increase rate on tumor recurrence. A prospective study is warranted to further validate the significance of the CA19-9 increase rate. Second, the interval between postoperative follow-ups was heterogenous, which may have given rise to a considerable bias in this study.

Conclusion

In conclusion, after the first elevation of postoperative CA19-9, tumor recurrence could be predicted based on the CA19-9 increase rate calculated using a follow-up CA19-9 measurement. It may be recommended that patient management differ based on the recurrence risk determined by the dynamics of postoperative CA19-9.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13304-024-01758-x>.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HI, and YT. The first draft of the manuscript was written by HI and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors have no competing interests to declare.

Ethics approval The current study was performed in compliance with the Declaration of Helsinki, and was approved by the ethical committee of our hospital (approval number 22507).

Informed consent Informed consent was obtained on a paper basis from each patient enrolled in this study.

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