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CA19-9 elevation as an indication to start salvage treatment in surveillance after pancreatic cancer resection

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ABSTRACT

Background: CA19-9 is the most commonly used tumor marker in the diagnosis, prognosis and surveillance of pancreatic cancer. We hypothesized that CA19-9 elevation can be taken as an indication to start salvage treatment in surveillance after resection.
Methods: From January 2014 and July 2017, 80 pancreatic cancer patients who underwent R0 surgical resection and received adjuvant chemotherapy were included.
Results: Twenty-six (32.5%) patients started salvage treatment at the time of CA19-9 elevation without radiological evidence of recurrence. Fifty-four (67.5%) patients treated conventionally before recurrence was confirmed by radiological examinations. Sixty (75%) patients had CA19-9 elevation that preceded radiographic recurrence by about 3 months. In the intervention group, the median DFS (23.6 months vs. 12.1 months, $P < 0.001$) and OS (28.1 months vs. 20.7 months, $P = 0.049$) were significantly longer than those in the control group.
Conclusions: CA19-9 elevation could preceded recurrence confirmed by radiographic examinations in most patients. Tumor marker-guided salvage treatment can significantly prolong disease-free survival and overall survival in patients under surveillance after pancreatic cancer resection.

Background

In 2018, it is estimated that there will be 458, 918 new cases of pancreatic cancer worldwide and almost all are expected to die from this high-risk disease [1,2]. Even in patients who have undergone curative pancreatic resection followed by adjuvant therapy, unfortunately, the median disease-free survival (DFS) is only 1 year, and high rates of recurrence make it difficult to improve the outcomes of patients receiving surgery [3–7].

Carbohydrate antigen 19-9 (CA19-9) is the most commonly used tumor marker in management of pancreatic cancer because it has utility in diagnosis, prognosis and surveillance [8–14]. When patients receive cytotoxic chemotherapy postoperatively, CA19-9 levels can reflect the clinical disease progression and its increasing value is often associated with a worse prognosis [14–17]. Regular radiographic examinations such as enhanced computed tomography (CT) have limited sensitivity in detecting small-volume recurrence, and postoperative CA19-9 elevation can precede radiographic evidence of recurrence by more than 6 months [18–21]. Therefore, elevating CA19-9 may become an indication to start salvage treatment. However, there is no evidence that "tumor marker-guided" salvage treatment can benefit patients with resectable pancreatic cancer.

Because postoperative CA19-9 elevation might precede the radiographic evidence of recurrence, the purpose of this study was to explore the impact of such an aggressive strategy on patients' survival and to determine whether salvage treatment should be established based only on CA19-9 elevation without radiographically proven recurrence.

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Materials and methods

Patients

The study cohort consisted of 80 pancreatic cancer patients who underwent R0 surgical resection and received adjuvant chemotherapy at Peking Union Medical College Hospital (PUMCH) between January 2014 and July 2017. All patients had comprehensive and detailed follow-up data with a rising postoperative CA19-9 level and recurrence diagnosed by radiological examinations in this study. Patients who were followed up at other institutions and did not have available recurrence data were excluded. Because CA19-9 is undetectable in Lewis antigen-negative individuals, patients whose CA19-9 levels were < 5 U/mL persistently were considered as Lewis antigen negative and were not analyzed [22]. Pancreatic endocrine tumors were not included in the current research.

When CA19-9 appeared to rise but the suspicion of recurrence was not confirmed by radiographic evaluations, patients who started salvage treatment immediately were included in group A as well as the intervention group. Patients who did not alter their existing schemes until there was radiographic evidence of recurrence were in group B. Patients with increasing tumor marker CA19-9 found at the time of radiological confirmation or after the confirmation were in group C. Both group B and C were defined as the control group because they did not consider CA 19-9 as an indication. The study protocol was approved by the ethics committee at PUMCH.

Treatment

A professional team in the department of general surgery performed all pancreatic resections and optimal adjuvant chemotherapy schemes were determined by doctors in the department of medical oncology. Tumor characteristics were assessed by experienced pathologists. TNM stages classification was based on the 7th edition of the American Joint Committee on Cancer (AJCC) classification system [23].

Follow-up

All patients followed up every three months. At each postoperative follow-up visit, CA19-9 tumor marker panel, necessary radiological examination (such as enhanced CT/MRI or occasional PET-CT), physical examination and routine laboratory examinations were performed. CA19-9 measurements were carried out by the laboratory department in PUMCH. In this study, we defined CA19-9 elevation as a value greater than the normally used upper limit (37 U/mL) with an increase over 30%. Furthermore, the CA19-9 level may be artificially elevated because of biliary infection or obstruction, which does not indicate progressed disease, so the CA19-9 value was not adopted when patients had abnormal bilirubin levels [24].

The follow-up data were updated until October 2018. Disease-free survival (DFS) was defined as the time from pancreatectomy to the first recurrence identified by radiological examinations or death. The time from CA19-9 elevation to radiographic recurrence was defined as interval. Overall survival (OS) was the time from the surgical resection to the latest follow-up date or death.

Statistical analysis

The statistical analyses were performed with IBM SPSS (version 25, IBM Corp., Armonk, NY, USA). Normality was tested with the Shapiro–Wilk test. Normally distributed continuous variables were assessed by Student's *t*-test and reported as the mean ± standard deviation. Categorical variables were evaluated with a Chi squared or Fisher's exact test. Otherwise, the Mann–Whitney rank-sum test was used. Different treatment strategies and their DFS, Interval and OS were shown with a Kaplan-Meier survival curve, and a log-rank test was applied to compare these curves.

Results

Patient characteristics

There were 80 patients included in this study. The intervention group (A) consisted of 26 (32.5%) patients who started their salvage treatment at the time of significantly increasing CA19-9 and negative radiological examinations. The control group (B + C) had 54 (67.5%) patients who were treated conventionally after metastases were confirmed by radiological examinations. The median follow-up time was 18.7 months. At the last follow-up, death was documented in 44 patients (55%) and 22 patients (27.5%) were still alive after a minimum follow-up of 12 months. Clinical characteristics of these patients are shown in Table 1. There was no

Table 1
Baseline clinical characteristics of patients.

Parameter	Intervention group	Control group		P value
	A (n = 26)	B (n = 34)	C (n = 20)	
Age (mean year ± S.D.)	58.4 ± 10.3	61.0 ± 11.0	51.8 ± 9.4	0.769
Sex (n)				0.741
Female	11	19	6	
Male	15	15	14	
Location (n)				0.253
Head	17	16	12	
Body/tail	9	18	8	
T (n)				0.924
2	7	14	0	
3	19	20	20	
N (n)				0.245
0	8	17	7	
1	18	17	13	
Stages (n)				0.204
I	2	9	0	
IIA	6	8	7	
IIB	18	17	13	
Differentiation (n)				0.652
Well/median	16	21	15	
Poor	10	13	5	
Pre-resection CA19-9 (n)				0.532
>370 U/mL	14	11	13	
<370 U/mL	12	23	7	
Post-resection CA19-9 (n)				0.756
>37 U/mL	13	15	10	
<37 U/mL	13	19	10	
Adjuvant chemotherapy (n)				0.455
Gemcitabine	18	18	12	
S-1	4	4	2	
Gemcitabine + S-1	2	6	3	
Others	2	6	3	
Recurrence site (n)				0.178
Local	6	5	4	
Regional	7	7	1	
Distant	8	18	12	
Multiple	5	4	3	
Salvage treatment (n)				0.058
Gemcitabine	3	1	2	
S-1	10	8	2	
Gemcitabine + S-1	6	3	4	
SOX/XELOX[a]	2	10	5	
Chemoradiotherapy	2	9	3	
Others	3	3	4	

[a] SOX: S-1 plus oxaliplatin; XELOX: capecitabine plus oxaliplatin.

statistically significant difference in prognostic factors between these two groups.

Most patients received single agent gemcitabine or S-1 as adjuvant therapy. Other additional treatment during adjuvant chemotherapy included chemoradiotherapy, oxaliplatin, irinotecan and paclitaxel-albumin. When patients started salvage treatment, most of them received gemcitabine or fluoropyrimidine based chemotherapy, which was different from their former regimen to overcome the drug resistance.

Rising tumor markers and radiological examination

The increasing tumor markers preceded the appearance of radiological signs of relapse in 60 of the 80 (75%) patients evaluated. In the remaining patients, no increase in the tumor marker was found at the time of relapse or the increased markers was contemporaneous with the radiological signs of metastases. The median interval between CA 19-9 elevation and radiological evidence of recurrence was 3.4 months.

Survival analysis

Patients who started salvage treatment only based on rising CA19-9 levels had a significantly longer median DFS than patients with treatment changes based on radiological examinations (23.6 months vs. 12.1 months, $P < 0.001$) (Fig. 1A). Compared with the A and B group, the interval from CA19-9 elevation to radiological confirmation was also significantly prolonged in patients with tumor marker guided salvage treatment (13.2 months vs. 3.5 months, $P < 0.001$) (Fig. 1B). Apart from the longer DFS, the median OS was prolonged in the intervention group (28.1 months vs. 20.7 months, $P = 0.049$) (Fig. 1C).

Discussion

According to the ASCO guidelines, rising CA19-9 levels usually precede the radiographic appearance of a recurrent disease, but the present data are insufficient to recommend the routine use of CA19-9 alone for monitoring responses to therapy without radiographic confirmation [25]. However, many studies have shown that there is a correlation between the patient's clinical benefits and tumor marker CA19-9 levels decline during chemotherapy for advanced pancreatic cancer, which means rising CA19-9 levels may serve as a negative predictive marker [14,26,27]. A recent study found that the time from CA19-9 elevation to radiographic recurrence ranged from 6 to 18 months [21]. No matter the type of cancer, the primary goal of surveillance after curative treatment is to detect the local or distant recurrence as early as possible and doctors can intervene to prolong the survival of patients. Therefore, rising CA19-9 levels during adjuvant chemotherapy might be helpful to consider salvage therapy, especially when the radiographic evidence of tumor recurrence is absent. However, there is still not enough evidence to support the apparent common practice that regular follow-up after surgery to identify earlier recurrence can improve the survival of patients [28–32]. Although the role of surveillance in patients with resected pancreatic adenocarcinoma is limited, CA19-9 measurement and follow-up CT scans with contrast every 3–6 months for 2 years after surgical resection are still category 2B recommendations according to NCCN guidelines.

Our current study suggested that CA19-9 can preceded the radiological appearance by about 3 months and tumor marker-guided early salvage therapy can delay disease progression and prolong overall survival of patients receiving resection. In patients who started their salvage treatment early, the median DFS and OS were prolonged compared with those patients who were treated only after recurrence was ascertained by radiological examinations. Approximately 80% of the recurrences of pancreatic cancer occur within two years after potentially curative treatment. When patients are informed about recurrence, they have a quite limited survival. This active adjuvant chemotherapy can slow down the disease progression and benefit patients with advanced pancreatic cancer, which deserves to improve the frequency of tumor marker assay in follow-up strategy because one CA19-9 assay costs only about 15 dollars in China.

Before this study, there was a heavily debated issue among doctors in the field of oncology; that is, whether salvage treatment based only on tumor marker should be carried out or not if the clinical characteristics of the patient are good and a CT scan is negative [33]. In addition to pancreatic cancer, tumor marker-guided treatment for other cancers has been reported. In breast cancer patients, CEA–TPA–CA15.3 tumor marker-guided salvage treatment can significantly prolong the DFS and OS in relapsing responsive patients [34,35]. Similarly, a longer OS of gastric cancer patients based on symptoms or tumor markers rather than CT was also reported [36]. However, some study showed that CEA combined with CT was not significantly different from regular CT in follow up of colorectal cancer [37]. A meta-analysis indicated that there was no survival benefit for patients with intensive follow-up after colorectal cancer resection, although more patients were treated with salvage treatment in intensive follow-up group [38]. In addition, when to initiate salvage therapy for prostate cancer patients with a prostate-specific antigen recurrence is controversial. Early hormonal treatment can only benefit patients with aggressive prostate cancer and a fast rising prostate-specific antigen, whereas in others it may be more harmful [39].

Surely, it is a highly individualized decision made by both doctor

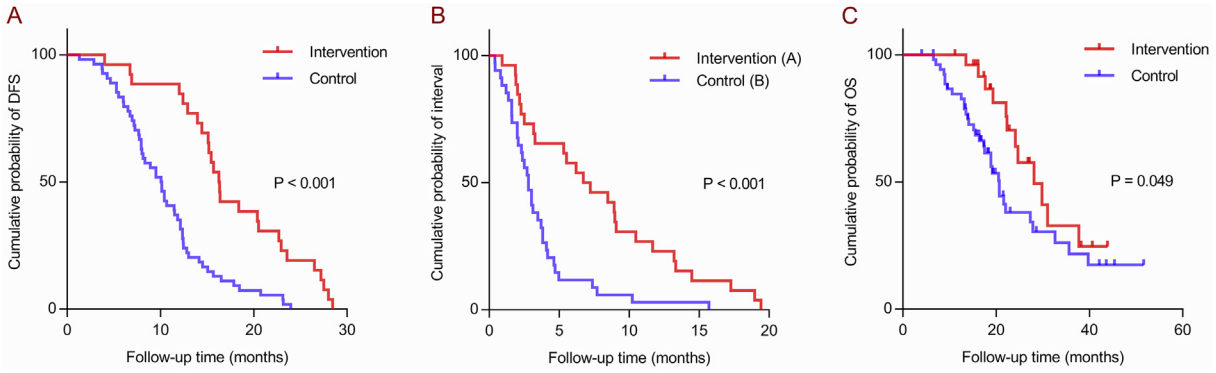

Fig. 1. Kaplan-Meier survival curve of DFS (A), Interval (B) and OS (C) in two groups.

and patient, but the clinical decision should be evidence-based. This retrospective study offers a better understanding of CA19-9 elevation and salvage treatment, which may be helpful for clinicians to adopt the most appropriate follow-up approach. Nowadays, liquid biopsy technology is rapidly emerging as a valuable tool in tracking therapeutic responses and our treatment strategy can be applied with this new technology in the future [40].

This study has several limitations. Our research was a retrospective and single-institutional study with a relatively small sample size. It is obvious that tumor marker-guided treatments are based on regular follow-up, and selection bias exists objectively. Future prospective, multi-center and randomized clinical trial validations are needed before generalizing the results to clinical practice. Our adjuvant chemotherapy was mainly based on gemcitabine or S-1 rather than modified FOLFIRINOX (oxaliplatin plus irinotecan with leucovorin and short-term infusional fluorouracil), which have been shown to be more effective than gemcitabine alone for advanced exocrine pancreatic cancer [41]. For future wide clinical application of this study, patients with modified FOLFIRINOX adjuvant chemotherapy should be included. Despite these limitations, the novelty and potential applicability of this paper is still exciting. During adjuvant therapy after potentially curative surgery, CA19-9 should be assayed every 1–3 months to predict possible recurrence from our study. We hope that our findings will stimulate randomized prospective trials on the early salvage treatment effect with pancreatic cancer and facilitate decision making on switching to an active strategy.

Conclusions

Our study demonstrated CA19-9 elevation could precede radiographic evidence of recurrence by about 3 months in 75% patients and tumor marker-guided salvage treatment can significantly prolong DFS and OS in patients under surveillance after pancreatic cancer resection. This research may help oncologists adopt the most appropriate follow-up approach and benefit pancreatic cancer patients.

Declarations

Authors' contributions

JRL, ZL, YJC and CMB conceived and designed the study. JRL, ZL and HXK collected the clinical data. JRL and YJC performed the statistical analyses. JRL wrote the manuscript. SZ, YJC and CMB reviewed and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no competing interests.

Availability of data and materials

The data of patients used in this study are available from the corresponding author upon reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the ethics committee of Peking Union Medical College Hospital. All included patients signed an informed consent form voluntarily.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.01.023.

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