



Case Series

Dramatic Regression of Metastatic Lesions Following Alkalization Therapy in Pancreatic Cancer: A Case Series

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Abstract: Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by rapid progression and poor prognosis, particularly in clinical stage IV disease. A hallmark of cancer metabolism, known as the Warburg effect, involves the production of lactic acid even under aerobic conditions, resulting in acidification of the tumor microenvironment. This acidic environment is associated with tumor progression and resistance to conventional therapies. Alkalinization therapy, including dietary modifications aimed at reducing the potential renal acid load (PRAL), seeks to counteract tumor acidity and modulate the tumor microenvironment. Case Description: Alkalinization therapy was administered to four patients with metastatic pancreatic cancer. The intervention consisted primarily of PRAL-reducing dietary modifications and oral supplementation with bicarbonate or citrate salts. The aim was to increase urinary pH and counteract tumor acidity. In all four cases, therapy was associated with marked regression of metastatic lesions. Conclusions: These findings suggest that alkalinization therapy may play a supportive role in the management of metastatic pancreatic cancer by altering the tumor microenvironment. Further clinical investigations are warranted to elucidate its therapeutic potential and underlying mechanisms.

Keywords: tumor microenvironment; tumor acidity; pancreas; alkalization therapy

1. Introduction

1.1. Background

Pancreatic ductal adenocarcinoma (PDAC) is characterized by rapid progression and is typically diagnosed at an advanced stage [1]. Despite advancements in the detection and management of pancreatic cancer, data from the United States National Cancer Institute indicate that the 5-year survival rate for clinical stage (cStage) IV pancreatic cancer remains only 3% [2]. Although treatment strategies have evolved, the prognosis and outcomes for patients diagnosed with pancreatic cancer have shown little improvement over the past 40 to 50 years [3].

The acidic tumor microenvironment (TME), driven by enhanced aerobic glycolysis (the Warburg effect), plays a critical role in cancer progression by promoting drug resistance, local invasion, and metastasis [4]. Unlike normal cells, which primarily generate energy through oxidative phosphorylation, cancer cells exhibit mitochondrial dysfunction and abnormalities in energy metabolism, relying instead on substrate-level phosphorylation and glycolysis [5,6].

A strong association has been established between increased intracellular pH (pHi) in cancer cells and the acquisition of multidrug resistance (MDR) [7–13]. In human lung cancer cells, an increase in pHi from 7.0 to 7.4



enhances resistance to adriamycin by approximately 2000-fold [14]. The drug tended to accumulate in cells with an acidic pHi, whereas its accumulation decreased in cells with an alkaline pHi. As a result, cancer cells adapt to the acidified TME and acquire aggressive, drug-resistant characteristics.

Membrane-bound transporters, such as Na⁺/H⁺ exchanger 1 (NHE-1) and H⁺/ATPase, play a pivotal role in maintaining the elevated intracellular pH of cancer cells while contributing to acidification of the TME. Modifying the pH gradient between the intracellular and extracellular compartments of cancer cells, specifically by alkalizing the extracellular environment, can suppress the activity of NHE-1 and H⁺/ATPase. Promoting intracellular acidification in cancer cells is essential for overcoming MDR and establishing effective treatment strategies. Angiogenesis inhibitors suppresses the activity of NHE-1 and H⁺/ATPase, thereby promoting the intracellular acidification in cancer cells [7,15,16].

1.2. Rationale and Knowledge Gap

“Alkalinization therapy”, which aims to achieve a urine pH of ≥ 7.5 through dietary modification with a low potential renal acid load (PRAL) and the intake of bicarbonates or citric acid [17], was proposed in this study. This approach emphasizes increased consumption of vegetables and fruits while minimizing the intake of meat and processed foods [17,18]. Although direct measurement of the acid-base balance within the body remains challenging in clinical practice, our previous study has reported that increased urine pH via alkalinization therapy is associated with improved survival and more favorable responses to chemotherapy in patients with various cancers [19]. Furthermore, a previous study showed that higher urine pH levels were associated with prolonged overall survival among patients with pancreatic cancer treated with potassium citrate and sodium citrate hydrate [20]. These findings suggest that urinary pH may function as an indirect, supportive marker of alterations in dietary acid load and net proton excretion, rather than a direct measure of the tumor microenvironment.

During alkalinization therapy, patients were instructed to follow a diet characterized by low PRAL values (Table 1). For adherence assessment, patients were asked to keep dietary records, which were reviewed and discussed during nutritional counseling sessions with a dietitian at each clinic visit. A minimum daily intake of 300 g of vegetables was recommended, while the consumption of beef and pork was restricted; fish or chicken were suggested as alternative sources of animal protein. If urine pH exceeded 7.5 through dietary measures alone, alkalinization therapy was continued without additional supplementation. However, if the target urine pH was not achieved, supplementation with 3–4.5 g/day of citric acid or 3–6 g/day of sodium bicarbonate was recommended [19,21].

In addition, several recent reports have examined intravenous ascorbic acid for cancer therapy in clinical settings, suggesting that combining chemotherapy with intravenous ascorbic acid may improve treatment outcomes and reduce the toxicities of chemotherapy and radiation therapy [22–25]. Therefore, among patients without G6PD deficiency who could continue intravenous infusions, intravenous ascorbic acid (25–50 g per dose) was administered in addition to alkalinization therapy at 1–2-week intervals for as long as tolerated.

Table 1. Alkalinization therapy protocol.

Component	Dietary with low PRAL; a minimum daily intake of 300 g of vegetables was recommended, while the consumption of beef and pork was restricted; fish, chicken, and eggs were suggested as alternative sources of animal protein. 3–4.5 g/day of citric acid 3–6 g/day of sodium bicarbonate
Target	Urine pH ≥ 7.5
Monitoring frequency	Ranges from 1 to 4 weeks

1.3. Objective

This case series present four cases of cStage IV pancreatic cancer in which metastatic lesions in the liver and lungs were significantly reduced following alkalinization therapy [26].

2. Case Presentation

2.1. Case 1

A 78-year-old woman was diagnosed with resectable pancreatic head cancer. Neoadjuvant chemotherapy with gemcitabine was initiated but discontinued after two cycles due to the development of obstructive suppurative pancreatitis. A subtotal stomach-preserving pancreaticoduodenectomy was subsequently performed. Postoperative

chemotherapy with tegafur/gimeracil/oteracil (TS-1) was attempted but discontinued after ten days due to severe loss of appetite. A follow-up computed tomography (CT) scan performed four months after surgery revealed multiple liver and lung metastases (Figure 1A–C). The patient visited Wada Clinic for further evaluation. Imaging at the time of consultation, two metastatic lesions in the liver and multiple nodular shadows in the lungs. Given the severe adverse events associated with previous chemotherapy regimens, anticancer drugs were not administered, and alkalization therapy was initiated. During alkalization therapy, a diet with low PRAL values was recommended [18]. In addition, oral citrate preparations and weekly intravenous infusions of 40 mL 7% sodium bicarbonate were administered. Furthermore, high-dose ascorbic acid at a dose of 25–50 g/day was also infused weekly.

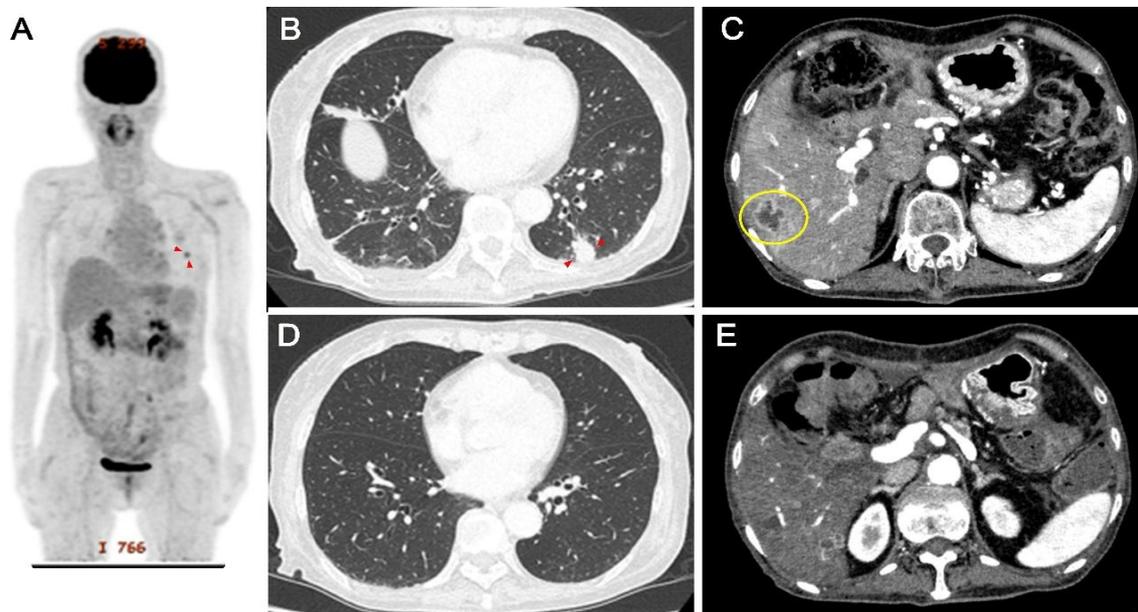


Figure 1. Lung metastasis was diagnosed four months after surgery for pancreatic cancer, as shown on positron emission tomography–computed tomography (PET-CT) (A) and chest CT (B), indicated by red arrows. Liver metastases are indicated by a yellow circle (C). Eleven months after the initiation of alkalization therapy, both lung and liver metastatic lesions resolved (D, E).

Eight months after initiating alkalization therapy, the patient’s urinary pH increased to 7.5–8.0 (Figure 2). A follow-up CT scan conducted 11 months after the alkalization therapy showed complete response, (Figure 1D,E). The patient has remained recurrence-free for four years since the initial diagnosis.

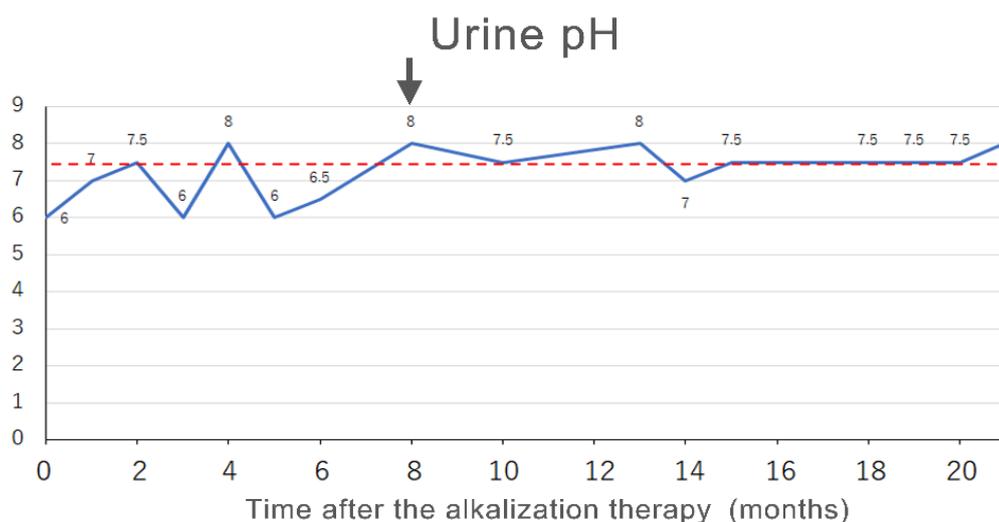


Figure 2. Trends in average urine pH following the initiation of alkalization therapy. Alkalization therapy continued throughout the period. Beginning eight months after the initiation of alkalization therapy (indicated by the arrow), the average urine pH was maintained at or above 7.5 (red dotted line).

2.2. Case 2

A 76-year-old man with abdominal pain underwent endoscopic ultrasound-guided fine-needle aspiration at another hospital. The patient's medical history included resolved hepatitis B infection and severe pancreatitis following endoscopic retrograde cholangiopancreatography. The patient was subsequently diagnosed with cStage IV invasive pancreatic cancer accompanied by liver metastasis and a malignant bile duct stricture (Figure 3A). Initially, a biliary stent was placed; however, the patient developed reflux cholangitis, which led to elevated levels of inflammatory markers. Consequently, a metal stent was installed. One month before admission to the Wada clinic, the patient began combination therapy with gemcitabine and nab-paclitaxel. Upon chemotherapy administration, the C-reactive protein level was 4.37 mg/dL, carcinoembryonic antigen (CEA) level was 4.6 ng/mL (Figure 4A), and urine pH was 6.0. During alkalinization therapy, the patient was instructed to follow a diet with low PRAL values [18]. Oral sodium bicarbonate was administered at a dose of 3.0 g/day. In addition, the gemcitabine dose was reduced by 65% (650 mg/m² once a week for 3 consecutive weeks followed by a one-week rest). Dietary recommendations involved limiting the intake of high-protein foods such as meat and cheese, while increasing the consumption of vegetables and fruits. One month after initiating alkalinization therapy, the patient's urine pH increased to 8.5 (Figure 4B). Four months later, the patient achieved partial response, that enhanced CT images revealed that the multiple liver metastases markedly decreased (Figure 3C).

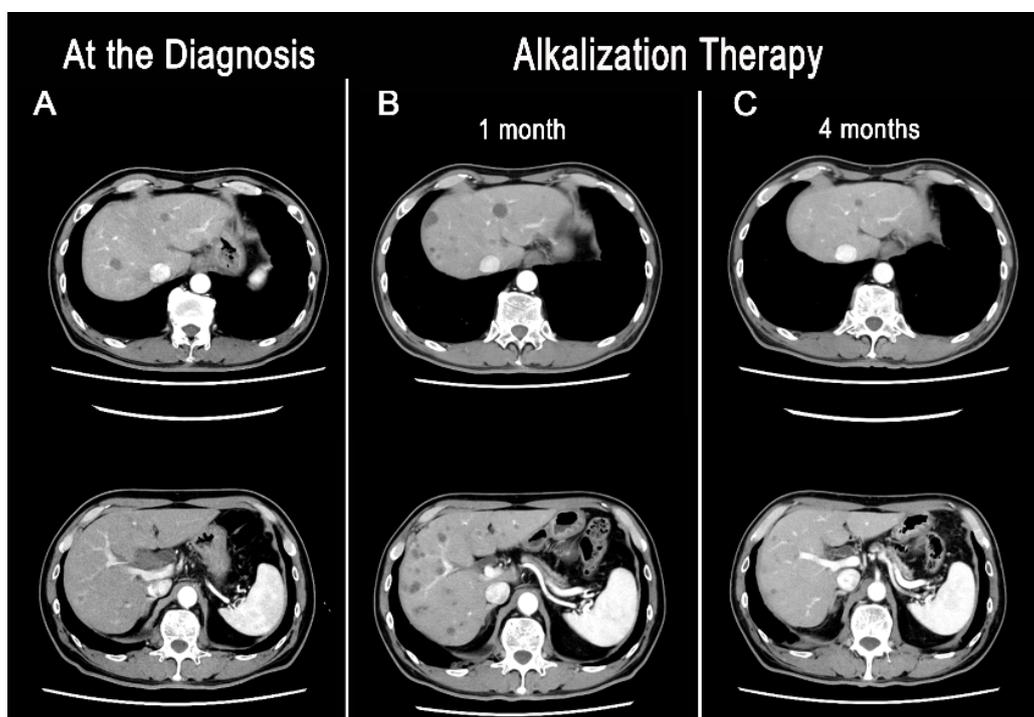


Figure 3. Contrast-enhanced computed tomography (CT) images before the initiation of alkalinization therapy (A), and at 1 month (B) and 4 months (C) after initiation. Despite a reduction in the gemcitabine dose to 65% following the start of alkalinization therapy, both the extent and size of liver metastases were reduced by the fourth month.

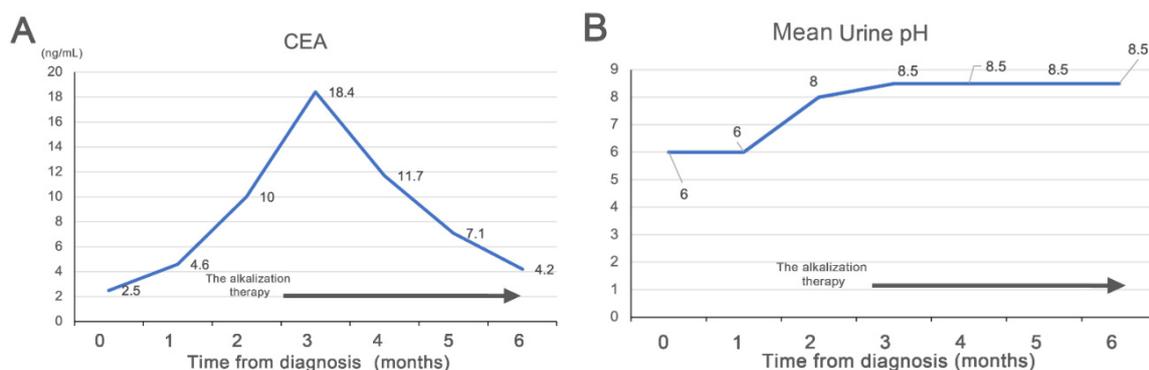


Figure 4. Time course of carcinoembryonic antigen (CEA) and urine pH levels following the initiation of alkalinization therapy. Within one month, urine pH exceeded 8.0, accompanied by a marked decrease in CEA levels.

2.3. Case 3

A 64-year-old woman was diagnosed with cStage IV pancreatic body cancer and liver metastasis (Figure 5A). Chemotherapy with gemcitabine and nab-paclitaxel was initiated; however, owing to the development of lower extremity edema and peripheral neuropathy, treatment was continued with gemcitabine monotherapy. The patient's urine pH was 5.0 on the first visit to the Wada clinic. After alkalization therapy with dietary modification, the patient's urine pH increased to 8.0 within one month. One year after initiating alkalization therapy, the dose of gemcitabine was reduced by 20% (800 mg/m² once a week for 3 consecutive weeks followed by a one-week rest). Enhanced CT performed 14 months after the initiation of alkalization therapy revealed a reduction in the size of the liver metastases (Figure 5B). At 24 months after the initiation of alkalization therapy, the patient was assessed as having achieved a complete response. The patient remains alive 10 years after the initial diagnosis.

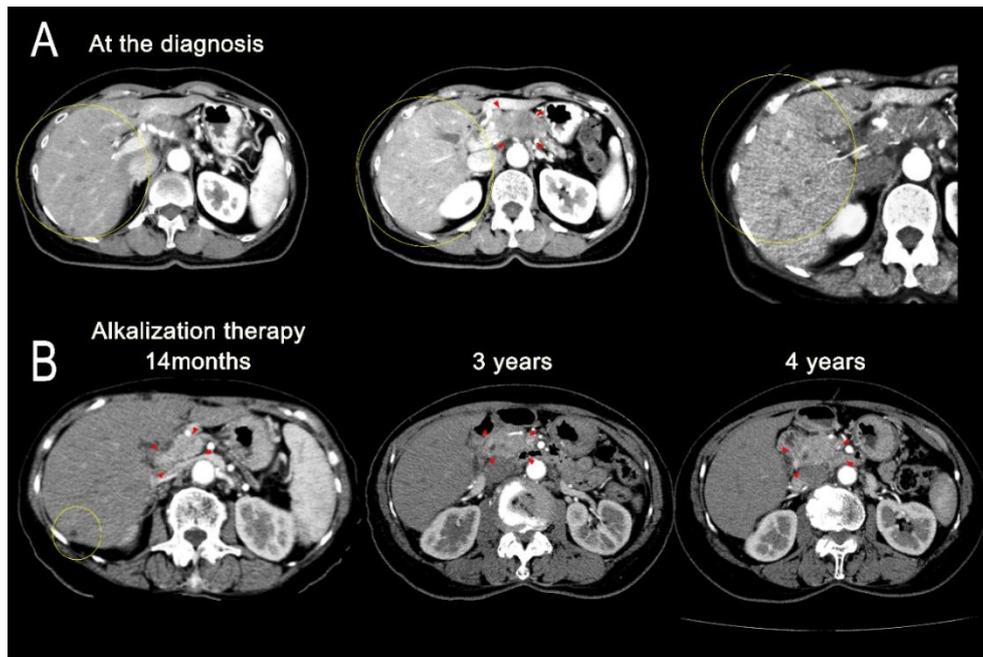
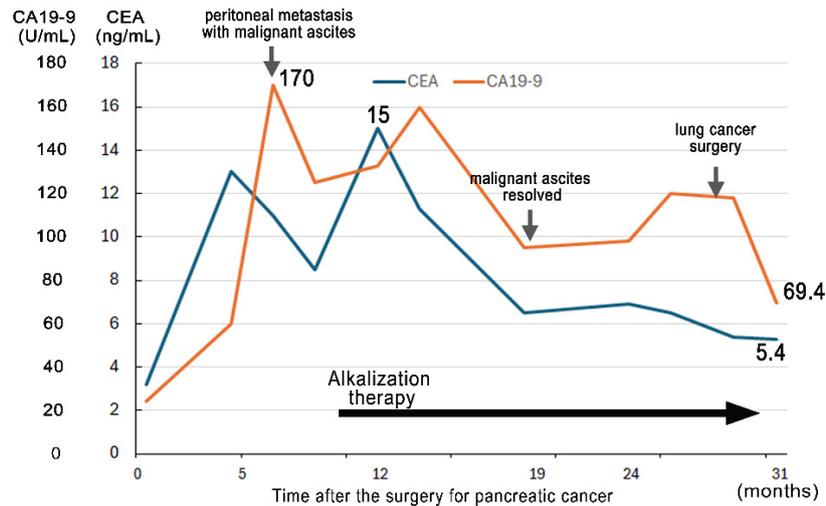


Figure 5. Contrast-enhanced computed tomography (CT) images at the time of pancreatic cancer diagnosis with multiple liver metastases (A) and after alkalization therapy (B). Liver metastases (yellow circles) decreased at 14 months after alkalization therapy. The primary pancreatic tumor, indicated by the red arrow, did not increase in size even four years after the initiation of alkalization therapy.

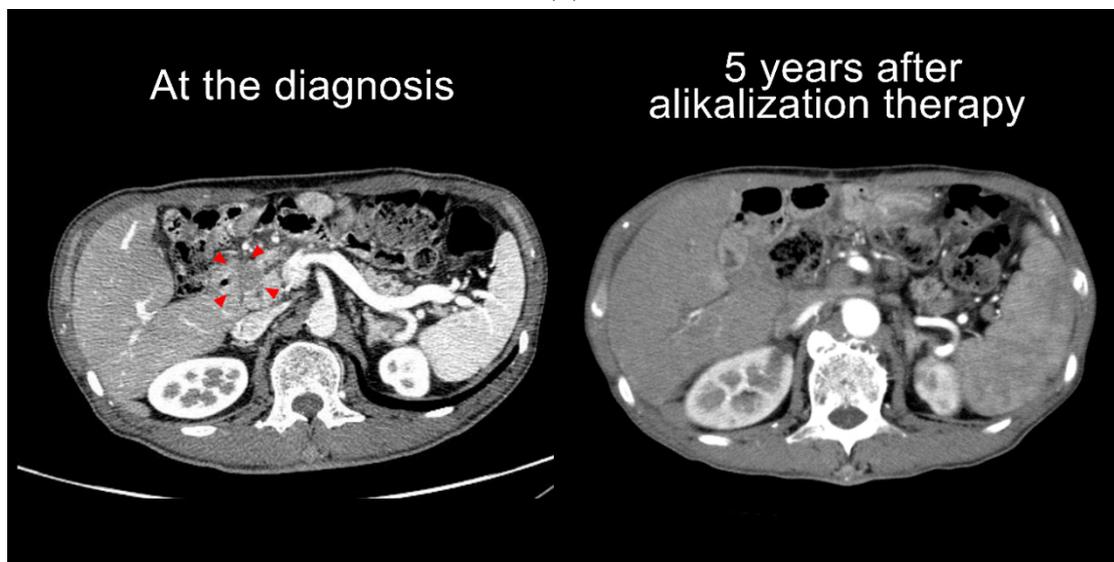
2.4. Case 4

A 70-year-old man underwent a pancreaticoduodenectomy for cStage IB pancreatic head cancer. However, the pathological diagnosis revealed stage III disease. Postoperative adjuvant chemotherapy was initiated with gemcitabine, followed by S-1 at a dose of 80 mg/day (administered for 2 weeks followed by a 1-week rest). Seven months after surgery, local recurrence at the primary pancreatic head cancer was detected, along with ascites, and peritoneal metastasis was diagnosed. CEA and carbohydrate antigen 19-9 (CA19-9) levels peaked at 15 ng/mL and 170 U/mL, respectively (Figure 6A). The patient then visited the Wada clinic, where alkalization therapy was initiated with a diet low in PRAL. The dose of S-1 was reduced to 60 mg/day. Six months after alkalization therapy, the ascites completely resolved. The reduced-dose S-1 regimen was discontinued 18 months after the initiation of alkalization therapy. However, contrary to the clinic's dietary guidance, the patient gradually shifted toward a higher-PRAL diet, consuming more meat and high-sugar foods. As a result, the urinary pH persistently decreased to as low as 5.5. At 28 months, the patient was diagnosed with regional left lung cancer. After surgical resection, the patient again strictly adhered to dietary modification in accordance with guidance for alkalization therapy. Consequently, 5 years after the alkalization therapy, the patient was assessed as a complete response (Figure 6B). The patient has survived for >10 years since the diagnosis.

The other four cases of cStage IV pancreatic cancer are detailed in Table 2. Consistent with the four previously described cases, these patients presented with liver and/or lung metastases and underwent alkalization therapy, which included a low-PRAL diet combined with oral administration of citric acid and sodium bicarbonate. From 6 months to 3 years after diagnosis, all patients remained alive, with tumor responses classified as either stable disease or partial response.



(A)



(B)

Figure 6. (A) Longitudinal changes in carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels and clinical course following surgery for pancreatic cancer. Initiation of alkalization therapy was followed by a decline in both tumor markers approximately six months later, coinciding with the resolution of malignant ascites. Two years after the initiation of alkalization therapy, a diagnosis of localized lung cancer was made; however, the patient retained sufficient operative tolerance and subsequently underwent successful surgical resection. (B) Contrast-enhanced computed tomography (CT) images at the diagnosis of pancreatic cancer (red arrows) and 5 years after alkalization therapy.

Table 2. Other four cases with clinical Stage IV pancreatic cancer.

Case	Diagnosis	Treatment	Alkalization therapy	Prognosis
60y, M	pancreatic tail cancer with liver and lymph node metastases (cStage IV)	GEM (2000 mg/body) + nab-PTX (250 mg/body): vasculitis and rash after 1st dose; GEM reintroduced at 60% dose	Citrate acid 3.8 g/day+ sodium bicarbonate 3 g/day and low PRAL dietary	SD at 12 months from diagnosis
58y, M	uncinate process cancer of the pancreas with liver metastases and para-aortic lymph node metastases (cStage IV)	GEM + nab-PTX; GEM continued at 70% dose after alkalization therapy Hyperthermia therapy	Low PRAL dietary	PR at 12months from diagnosis
88y, F	Pancreatic tail tumor with lymph nodes and lung metastases (cStage IV)	Hyperthermia therapy	Citrate acid 2.6 g/day + sodium bicarbonate 3 g/day, and low PRAL dietary	SD at 10 months from diagnosis
78y, F	Pancreatic cancer with left lung, left adrenal metastasis (cStage IV)	PPPD; 1 yr later, thoroscopic wedge resection	Citrate acid 2.6g/day + sodium bicarbonate 3 g/day, and low PRAL dietary	SD at 3 years from diagnosis

3. Discussion

Up to 80% of patients with PDAC may experience disease recurrence within five years, and up to 60% may experience recurrence within two years [27–29]. A recent study of 718 resected PDAC cases reported a recurrence rate of 72% after a median follow-up of 32 months. The median overall survival (OS) was 21 months, and the median post-recurrence survival (PRS) was 9 months. Prognostic factors associated with shorter PRS include age, multiple-site recurrence, and the presence of symptoms at the time of recurrence [30]. A real-world retrospective study of metastatic pancreatic cancer further demonstrated that patients with liver-only metastases had a shorter median OS than those with lung-only metastases, regardless of first-line standard-of-care therapy [31]. Notably, all cases presented in this case series exhibited potentially poor prognostic factors.

Grounded in this mechanistic framework, preclinical experiments in murine models have shown an association between intratumoral pH and urinary pH during alkalization therapy, as well as enhanced chemotherapeutic efficacy. In the Colon26 tumor-bearing mouse model, sodium bicarbonate treatment potentiated the anti-tumor activity of doxorubicin [32]. Likewise, administration of sodium–potassium citrate augmented the therapeutic effect of TS-1, an oral 5-fluorouracil prodrug enhanced in a Panc-1 pancreatic cancer xenograft model [33]. In both studies, these alkalizing agents were accompanied by increased blood HCO_3^- levels and elevated urinary pH. Furthermore, these findings suggest that alkalization therapy may be compatible with concomitant chemotherapy and may enhance its antitumor efficacy, thereby maintaining therapeutic benefit even after chemotherapy dose reduction.

Our two previous reports have demonstrated the effectiveness of alkalization therapy in PDAC. A case-control study compared 36 patients with metastatic or recurrent PDAC who underwent alkalization and chemotherapy with 89 patients who received chemotherapy alone. The results indicated that the median OS was significantly longer in the alkalization group than in the control group (15.4 vs. 10.8 months; $p < 0.005$) [34]. Another retrospective analysis involving 28 patients with metastatic or recurrent PDAC who underwent combined chemotherapy and alkalization therapy found that patients with urine pH > 7.0 had significantly longer OS compared with those with urine pH ≤ 7.0 , with median survival times of 16.1 months versus 4.7 months, respectively ($p < 0.05$) [35].

In addition, alkalization therapy and intravenous ascorbic acid has shown favorable outcomes in patients with small-cell lung cancer [36]. Ascorbic acid is taken up by cancer cells via glucose transporters and subsequently oxidized to dehydroascorbate, which inhibits glyceraldehyde 3-phosphate dehydrogenase. This inhibition may suppress activated glycolysis, particularly in cancer cells exhibiting high glycolytic metabolism [37].

Although direct measurement of acid-base balance remains challenging in clinical practice, urine pH may serve as an indirect marker. Welcher et al. reported that higher urine pH levels are associated with greater intake of fruit and vegetable and lower consumption of meat, indicating that urine pH is a useful biomarker for assessing systemic acid-base status [38]. We demonstrated that increased urine pH via alkalization therapy correlates with improved survival and better responses to chemotherapy in various malignancies [17,19,36].

This case series has several limitations. First, urinary pH is an indirect measure of systemic acid–base balance and dietary acid load. Therefore, any link between urinary pH and the pH of the tumor microenvironment remains hypothetical in this case series. We did not directly measure intratumoral or peritumoral pH and thus cannot confirm whether alkalization therapy altered tumor microenvironmental acidity. Second, prognosis may have been influenced by potential confounders, including prior chemotherapy exposure and intercurrent infections. These factors should be accounted for in future prospective observational studies evaluating the effects of alkalization therapy. Further investigation is necessary to clarify the correlation between the extracellular pH of cancer cells and urine pH, including detailed evaluations using patient-derived samples and in vivo experiments.

4. Conclusions

In this case series, the patients presented with multiple recurrent lesions and advanced age, both factors associated with shorter PRS, indicating a poor prognosis. However, the recurrent lesions resolved following sustained elevation of urine pH through dietary modifications and oral alkalizing agents, despite the absence of postoperative chemotherapy. The patients have remained alive for more than four years after diagnosis. These findings suggest that systemic pH modification, monitored via urine pH, may have contributed to the favorable outcomes observed.

Author Contributions

Conception and design: S.K. Administrative support: S.K. Provision of study materials or patients: All authors; Collection and assembly of data: S.K. Data analysis and interpretation: S.K. and H.W. Manuscript writing: All authors. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Japan-Multinational Trial Organization (JMTO-056). The studies involving human participants were reviewed, and written informed consent was obtained from the individual(s) and minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Informed Consent Statement

Informed consent was obtained from all individuals included in this study.

Conflicts of Interest

Given the role as Editor-in-Chief, Hiromi Wada had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal. The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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