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Cancer can be suppressed by alkalizing the tumor microenvironment: the effectiveness of “alkalization therapy” in cancer treatment

https://doi.org/10.1515/oncologie-2024-0673
Received December 17, 2024; accepted April 1, 2025;
published online May 26, 2025

Abstract

Objectives: The abnormal metabolism of cancer cells, referred to as the Warburg effect, creates acidic tumor microenvironments (TME) that can contribute to treatment resistance and cancer progression. “Alkalization therapy”, which involves dietary changes, aims to reduce acidity by lowering the potential renal acid load. This study aims to analyze 5-year survival rates of cancer patients undergoing alkalization therapy and compare survival rates among various urine pH levels.

Methods: A total of 1,100 patients with stage IV cancers who first visited Karasuma Wada Clinic between January 2014 and December 2023 were retrospectively analyzed. The Kaplan–Meier method, log-rank test, and Cox proportional hazards model were used for statistical analyses.

Results: The overall 5-year survival rate was 37.7 %, including 7.9 % for pancreatic cancer, 44.3 % for breast cancer, and 48.6 % for non-small cell lung cancer (NSCLC). For pancreatic cancer, urine pH was the only significant prognostic factor, with a hazard ratio of 0.55 (95 % CI: 0.36–0.83, p=0.004). The 5-year survival rates of patients categorized by urine pH levels (pH≤5.5, 5.5<pH<7.5, and pH≥7.5) showed significant differences in patients with pancreatic and breast cancer (p<0.0001 and p=0.009, respectively). For NSCLC patients, a cutoff urine pH of 5.5 (≤5.5 vs. >5.5) showed a significant difference in overall survival (p=0.0434).

Conclusions: Alkalization therapy is a promising cancer treatment that complements standard therapies. Raising urine pH may optimize TME and enhance survival outcomes.

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Keywords: tumor microenvironment; tumor acidity; pancreatic cancer; breast cancer; non-small cell lung cancer; alkalization therapy

Introduction

Specific somatic mutations have long been recognized to transform normal cells into cancerous cells, primarily through activating proto-oncogenes and inducing the loss of function of genes [1]. However, the direct role of somatic mutations in carcinogenesis [2] and the process by which normal cells become cancerous are still areas of ongoing research.

Otto Warburg, a pioneer in cancer metabolism, first reported that cancer cells undergo abnormal metabolism. Warburg identified that, unlike normal cells, which mainly generate energy through oxidative phosphorylation, cancer cells rely substantially on substrate-level phosphorylation and glycolysis [3, 4]. This characteristic, known as the Warburg effect, has been shown to play an essential role in the treatment resistance of cancer cells [5, 6]. Warburg effect was referenced in an intriguing study by Goldblatt and Cameron, who demonstrated that rat myocardial fibroblasts exposed to intermittent anaerobic conditions undergo tumorigenic changes [7].

Through the above processes, the metabolism of cancer cells deviates from typical metabolic regulation, which then promotes aerobic glycolysis. The activation of this “glycolytic switch” is a crucial factor that promotes tumorigenesis and is observed in approximately 70–80 % of human cancers [8]. This metabolic reprogramming, driven by factors such as hypoxia-inducible factor-1 overexpression, oncogene activation (e.g., *cMyc*, *Ras*), and the loss of tumor suppressor genes (e.g., *p53*, *PTEN*), is a hallmark of cancer [8].

The tumor microenvironment (TME), which comprises stromal cells, including fibroblasts, macrophages, and lymphocytes, surrounds the tumor mass and forms the tumor stroma. In the TME, factors such as hypoxia, low pH, and low glucose concentration promote tumor growth [9, 10]. The excess protons generated by aerobic glycolysis are expelled from the cancer cell by pumps, such as sodium-hydrogen

exchanger isoform 1 (NHE-1), creating a highly acidic microenvironment around the cancer cells [10, 11]. Whereas the intracellular pH (pHi) of normal cells is neutral (ranging from 6.9 to 7.1), the pHi of cancer cells tends to be alkaline (between 7.2 and 7.7) [12, 13]. The protons in the acidic TME recruit bone marrow-derived suppressor cells, resulting in a substantial increase in inflammatory cells, such as neutrophils and macrophages [14–18].

The acidified TME substantially affects tumor progression, and leads to the following characteristics [19–23]:

i) Increased malignancy;
ii) Increased activation of cell proliferation and division cycles;
iii) Expression and activation of genetic abnormalities and oncogenes;
iv) Activation of cell proliferation factors;
v) Increased glycolytic activity;
vi) Activation of DNA synthesis;
vii) Activation of cell migration;
viii) Stimulation of angiogenesis;
ix) Increased metastatic potential;
x) Activation of multidrug resistance genes.

A strong association between increased pHi and the acquisition of multidrug resistance (MDR) has also been established [10], highlighting the importance of pH in cancer treatment. It has been shown in human lung cancer cells that an increase in pHi from 7.0 to 7.4 enhances resistance to adriamycin by approximately 2,000-fold [24]. The drug tended to accumulate in cells with acidic pHi, while conversely, it decreased its accumulation in cells with alkaline pHi.

As a result, cancer cells adapt to the acidified TME, acquiring more aggressive and drug-resistant characteristics.

These findings suggest that promoting intracellular acidification in cancer cells is essential for overcoming MDR, and for establishing more effective treatment strategies. Targeting membrane-bound transporters, such as NHE-1 and H^+/ATPase to induce intracellular acidification presents a promising therapeutic approach. Indeed, angiogenesis inhibitors have been found to suppress the activity of NHE-1 and H^+/ATPase, thereby promoting the intracellular acidification of cancer cells [10, 11, 25].

The concept of "alkalization therapy" has gained attention as a method for alkalizing the extracellular environment, which subsequently induces intracellular acidification by reducing the activity of NHE-1 and H^+/ATPase. Through "alkalization therapy," we aim to modify the extracellular environment of cancer cells via dietary alkalization by the intake of bicarbonate or citrate salts, aiming to maintain a urine pH of 7.5 or higher [12]. In mouse cancer models, bicarbonate intake has been shown to increase extracellular pH, resulting in the reduced metastatic potential of cancer cells and tumor size [26, 27]. These findings suggest that alkalization therapy can enhance the efficacy of existing cancer treatments [24, 28].

Alkalization therapy focuses on foods that promote alkalization. It is important to minimize the intake of meat and processed foods to reduce acid load and support a systemic alkaline environment [29]. Our research group has shown that improving patients' body constitution and changing the TME to an alkaline state can improve the efficacy of cancer treatment [30]. However, no previous studies have analyzed the long-term prognosis of cancer patients who undergo alkalization therapy. Hence, this study aims to analyze the 5-year survival rate of cancer patients undergoing alkalization therapy and to clarify the differences according to their urine pH levels.

Analysis methods

Study design

This study was a retrospective analysis conducted to evaluate the 5-year survival rates and the long-term potential effects of alkalization therapy on patients with stage IV metastatic cancers. The analysis was conducted on 1,110 cases of patients with stage IV cancers who first visited the Karasuma Wada Clinic between January 2014 and December 2023 (Figure 1). The observation period extended from the first visit until April 30, 2024, during which patients continued to visit the clinic. Among them, there were 127 patients with stage IV pancreatic cancer, 131 patients with stage IV breast cancer, 253 patients with stage IV non-small cell lung cancer (NSCLC), and 599 patients with other stage IV cancers. The average urine pH of each patient was measured

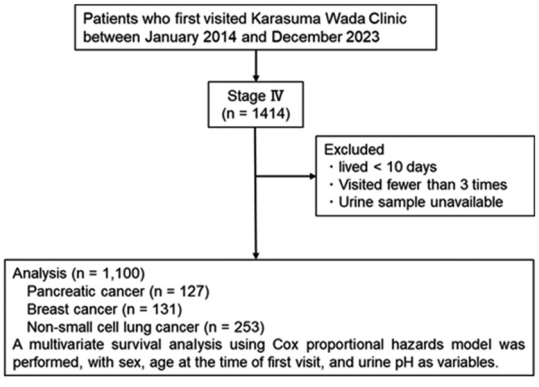

Figure 1: Flow chart for patient inclusion and exclusion.

from the first visit to the last visit. Patients who survived more than 10 days from the initial visit, visited the clinic at least 3 times, and provided urine samples on each visit were included in the study. Data was gathered from the clinic's medical records. All patients received alkalization therapy, which included an alkalizing diet and the oral administration of alkalizing agents, such as sodium bicarbonate and citric acid. The patients attended at least three outpatient visits and followed the alkalization therapy protocol outlined below. During each visit, patients received instruction on the specifics of the alkalization therapy. Based on the authors' previous finding that an increase in pH by at least 1 unit is associated with improved prognosis [31], the patients were divided into three urine pH groups, namely, pH 5.5 or less (Group 1), more than pH 5.5 but less than 7.5 (Group 2), and pH 7.5 or more (Group 3), and their 5-year survival rates were analyzed.

The study was conducted in accordance with the Declaration of Helsinki, approved by the Institutional Review Board of the Japan Chapter of the American College of Chest Physicians (approval number 2023-1), and has been registered with UMIN Clinical Trials under registration number UMIN000052333 (date of the registration, 21 September 2023).

The analysis was conducted on 1,110 cases of patients with stage IV cancers who first visited the Karasuma Wada Clinic between January 2014 and December 2023. The observation period extended from the first visit until April 30, 2024, during which patients continued to visit the clinic. Patients with 3 cancer types (pancreatic, breast, and non-small cell lung cancer) were analyzed.

Alkalization therapy

During treatment with alkalization therapy, the patient was instructed to follow a diet low in potential renal acid load (PRAL) values. Patients were recommended to consume a minimum of 300 g of vegetables daily, to refrain from the consumption of beef and pork, and to incorporate fish or chicken as alternative sources of animal protein. If the patient's urine pH exceeded 7.5 owing to diet alone, alkalization therapy was continued with diet alone. However, if the urine pH did not reach this level, the intake of 3–4.5 g/day of citric acid or 3–6 g/day of sodium bicarbonate was recommended [12, 30]. Although directly measuring the acid-base balance within the body remains challenging in clinical practice, we previously reported that increased urine pH via alkalization therapy correlated with improved survival and more favorable responses to chemotherapy in patients with various cancers [30]. Furthermore, a previous study demonstrated that higher urine pH levels are associated with greater fruit and vegetable intake, indicating the potential of urine pH as a useful biomarker for changes in dietary proton excretion [32]. Therefore, urine pH was used as a surrogate biomarker for assessing systemic acid-base balance.

Statistical analysis

Average urine pH values were measured for each patient across all collected urine samples. The Kaplan–Meier method, log-rank test, and Cox proportional hazards model were used to assess survival rates and differences among pH levels. Statistical analyses were performed using the statistical program JMP Pro for Windows (version 13.0, SAS Institute Inc., Cary, NC, USA). A p-value of less than 0.05 was considered to indicate a statistically significant difference between groups. Owing to the absence of patients with comparable backgrounds, a direct comparison between patient groups was not possible. However, data regarding the 5-year survival rate from the National Cancer Center of Japan has been cited for reference purposes [33]. The information from the National Cancer Center can be accessed at https://ganjoho.jp/reg_stat/statistics/stat/cancer/1_all.html.

Results

The 5-year survival rates of patients with stage IV cancers were analyzed. As shown in Table 1 and Figure 2A, there were 1,110 patients with stage IV cancer at Wada Clinic, and the 5-year survival rate was 37.7 %, while it was 15.7 % of 109,308 patients in the report from the National Cancer Center of Japan.

On multivariate survival analysis using the Cox proportional hazards model, in which urine pH, sex, and age at

Table 1: 5-year survival rates for stage IV cancers as reported by Wada Clinic and the National Cancer Center.

	Wada Clinic		National Cancer Center
	Pts, n	5YSR, %	5YSR, %
All cancers	1,110	37.7 %	15.7 %
Pancreatic cancer	127	7.9 %	1.8 %
Breast cancer	131	44.3 %	39.3 %
NSCLC	253	48.6 %	6.4 %

At Wada Clinic, there were a total of n=1,110 cases across all cancer types, including 127 cases of pancreatic cancer, 131 cases of breast cancer, and 253 cases of NSCLC. Pts, patients; 5YSR, 5-year survival rate; NSCLC, non-small cell lung cancer.

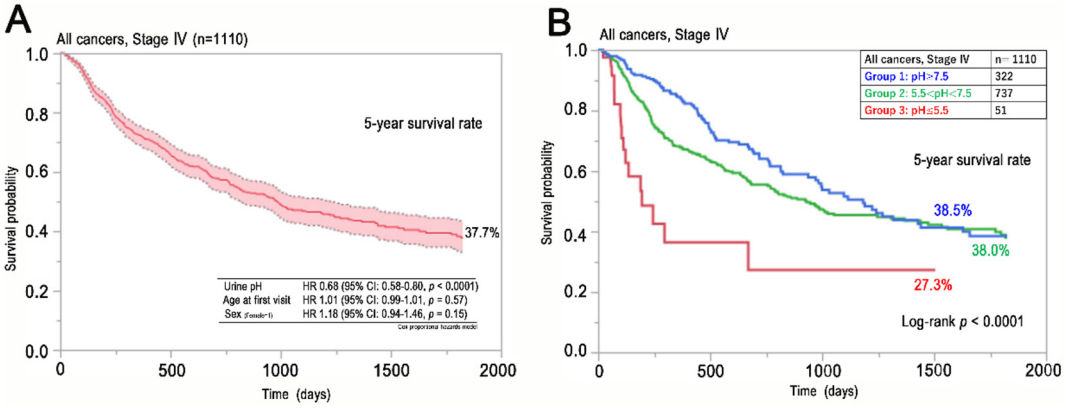

Figure 2: Kaplan-Meier survival curve for the Wada Clinic recorded 1,110 patients with stage IV cancer of various types. (A) Shows the 5-year survival rate for all cancers at stage IV of 37.7 %. The National Cancer Center Japan reported a 5-year survival rate of 15.7 %. The inserted table shows the multivariate survival analysis using the Cox proportional hazards model. The solid line in the graph represents the point estimate of the survival rate, and the dashed lines indicate the 95 % confidence interval. (B) Shows the 5-year survival rates of patients with stage IV cancers categorized by urine pH levels as follows: Group 1 (pH≥7.5), Group 2 (5.5<pH<7.5), and Group 3 (pH≤5.5). Groups 1 and 2 demonstrated higher survival rates than Group 3.

first visit were included as explanatory variables, high urine pH was the only statistically significant prognostic factor, with a hazard ratio (HR) of 0.68 (95 % confidence interval (CI): 0.58–0.80, p<0.0001), indicating that a 1-unit increase in urine pH corresponds to a 32 % reduction in the risk of death. It is important to note that the analysis does not specify a particular qualification or range for urine pH. Most patients at Wada Clinic have been diagnosed as having stage IV cancer, and most of these individuals have been referred to our clinic for palliative care after having undergone all standard cancer treatments.

As shown in Figure 2B, the association between urine pH and survival rate for patients with all types of stage IV cancer was analyzed. In the 51 patients in Group 3 (pH≤5.5), the 5-year survival rate had not yet been reached at the time of the analysis. The 5-year survival rate for the 737 patients in Group 2 (5.5<pH<7.5) was 38.0 %, and for the 322 patients in Group 1 (pH≥7.5) was 38.5 %. The log-rank test showed a significant difference between urine pH levels among the 3 groups (p<0.0001). Additionally, when the analysis was performed using a urine pH cutoff point of 5.5 (≤5.5 vs. >5.5), a significant difference in overall survival was observed between the 2 groups (p<0.0001). When the analysis was performed using a urine pH cutoff point of 5.5 (≤5.5 vs. >5.5), a significant difference in overall survival was observed between the 2 groups (p<0.0001).

The 5-year survival rate for patients with stage IV pancreatic cancer was 7.9 %, as shown in Figure 3A. It is well known that the prognosis of stage IV pancreatic cancer patients is extremely unfavorable [31, 34]. Indeed, the National Cancer Center of Japan reported a 5-year survival rate of 1.8 %. On multivariate survival analysis using the Cox proportional hazards model, in which urine pH, sex, and age at first visit were included as explanatory variables, urine pH was the only statistically significant prognostic factor, with an HR of 0.55 (95 % CI: 0.36–0.83, p=0.004), indicating that a 1-unit increase in urine pH corresponds to a 45 % reduction in the risk of death, confirming that a higher urine pH is associated with improved survival. It is important to note that the analysis does not provide a specific qualification or range for urine pH. Figure 3B shows the 5-year survival rates for patients with stage IV pancreatic cancer, categorized by urine pH levels. There were 10 patients in Group 3 (pH≤5.5), and all individuals either died or discontinued their visits by day 122. There were 93 patients in Group 2 (5.5<pH<7.5), and the 5-year survival rate for this group was 8.1 %. There were 24 patients in Group 1 (pH≥7.5), and the 5-year survival rate was 9.6 %. The log-rank test demonstrated a significant difference in survival rates among the 3 groups (p<0.0001). Additionally, when the analysis was performed using a urine pH cutoff point of 5.5 (≤5.5 vs. >5.5), a significant difference in overall survival was observed between the 2 groups (p<0.0001).

Figure 4A shows the 5-year survival rate for patients with stage IV breast cancer. Whereas this was reported to be 39.3 % by the National Cancer Center of Japan, it was 44.3 % for the 131 patients at Wada Clinic. Multivariate analysis using the Cox proportional hazards model, in which urine pH, sex, and age at first visit were included as explanatory variables, demonstrated that none of these variables significantly correlated with survival. Figure 4B shows the 5-year survival rates for patients with stage IV breast cancer, categorized by their urine pH levels. In Group 3 (pH≤5.5), all individuals either died or discontinued their visits by

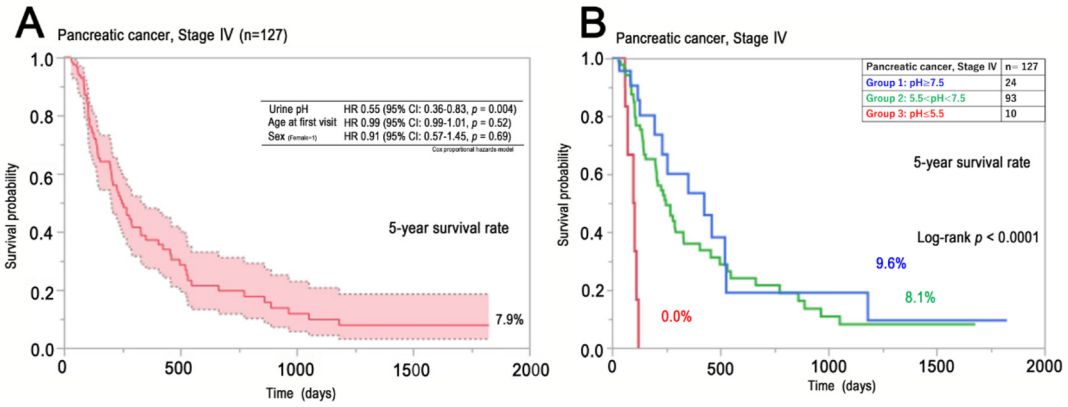

Figure 3: Kaplan-Meier survival curve for the Wada Clinic recorded 127 patients with stage IV pancreatic cancer. (A) Shows the 5-year survival rate for stage IV pancreatic cancer of 7.9 %. The National Cancer Center of Japan reported a 5-year survival rate of 1.8 %. The solid line in the graph represents the point estimate of the survival rate, and the dashed lines indicate the 95 % confidence interval. The inserted table shows the multivariate survival analysis using the Cox proportional hazards model. (B) Shows the 5-year survival rates of patients with stage IV pancreatic cancer, categorized by urine pH levels as follows: Group 1 (pH≥7.5), Group 2 (5.5<pH<7.5), and Group 3 (pH≤5.5). The log-rank test showed a significant difference between the 3 groups. Group 3 with a urine pH≤5.5 and the other 2 groups. Additionally, when the analysis was performed using a urine pH cutoff point of 5.5 (≤5.5 vs. >5.5), a significant difference in overall survival was observed between the 2 groups (p<0.0001).

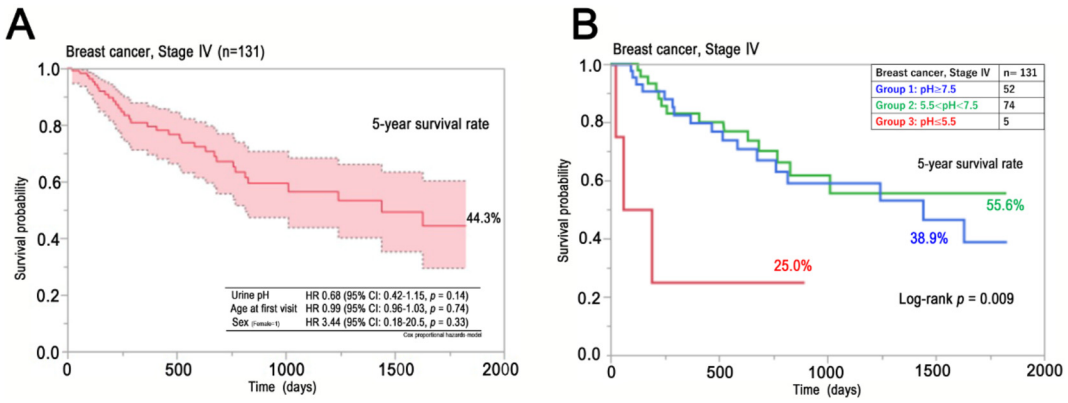

Figure 4: Kaplan-Meier survival curve for the Wada Clinic recorded 131 patients with stage IV breast cancer. (A) Shows the 5-year survival rate of 44.3 %. The National Cancer Center of Japan reported a 5-year survival rate of 39.3 %. The inserted table shows that the multivariate survival analysis did not identify urine pH as a statistically significant prognostic factor. The solid line in the graph represents the point estimate of the survival rate, and the dashed lines indicate the 95 % confidence interval. (B) Shows 5-year survival rates of patients with stage IV breast cancer, categorized by urine pH levels as follows: Group 1 (pH≥7.5), Group 2 (5.5<pH<7.5), and Group 3 (pH≤5.5). Group 1 (urine pH≥7.5) demonstrated the highest survival rate.

893 days after their first visit. Group 2 (5.5<pH<7.5) included 74 patients, and the 5-year survival rate was 55.6 %. Group 1 (pH≥7.5) included 52 patients, and the 5-year survival rate was 38.9 %. The log-rank test demonstrated a significant difference in survival rates among the 3 groups (p=0.009). Additionally, when the analysis was performed using a urine pH cutoff point of 5.5 (≤5.5 vs. >5.5), a significant difference in overall survival was observed between the 2 groups (p=0.0032).

The 5-year survival rate for patients with stage IV NSCLC is shown in Figure 5A. There were 253 patients with stage IV NSCLC at Wada Clinic during the study period, and the 5-year survival rate was 48.6 %. On the other hand, the 5-year survival rate at the National Cancer Center of Japan was 6.4 %. Multivariate analysis using the Cox proportional hazards model, in which urine pH, sex, and age at first visit were included as explanatory variables, demonstrated that none of these variables significantly correlated with survival. Figure 5B shows the 5-year survival rates of stage IV NSCLC patients stratified into 3 groups according to their urine pH level. Group 3 (pH≤5.5) included 9 patients, and on the 670th day, 1 patient died, and the estimated 5-year survival rate became 0 %. Group 2 (5.5<pH<7.5) included 171 patients, and the 5-year survival rate was 51.9 %. Group 1

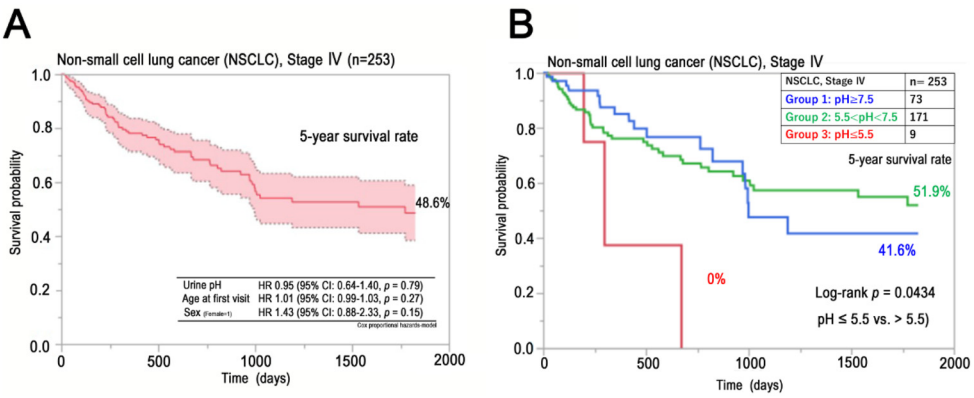

Figure 5: Kaplan-Meier survival curve for the Wada Clinic recorded 253 patients with stage IV non-small cell lung cancer (NSCLC). (A) Shows a 5-year survival rate of 48.6 %. The National Cancer Center of Japan reported a 5-year survival rate of 6.4 %. The inserted table shows that the multivariate survival analysis did not identify urine pH as a statistically significant prognostic factor. The solid line in the graph represents the point estimate of the survival rate, and the dashed lines indicate the 95 % confidence interval. (B) Shows the 5-year survival rates for patients with stage IV NSCLC, categorized by urine pH levels as follows: Group 1 (pH≥7.5), Group 2 (5.5<pH<7.5), and Group 3 (pH≤5.5).

(pH≥7.5) included 73 patients, and the 5-year survival rate was 41.6 %. There were no significant differences in survival rates among the 3 groups (p=0.13). However, when the analysis was performed using a urine pH cutoff point of 5.5 (≤5.5 vs. >5.5), a significant difference in overall survival was observed between the 2 groups (p=0.0434), suggesting that higher urine pH levels are associated with a more favorable prognosis.

Discussion

Clinical impact of urinary pH

In this study, we conducted the first analysis to our knowledge of the effect of alkalization therapy on the long-term survival of patients with stage IV cancer, assessing variations in survival rates based on cancer type and urinary pH levels. Notably, in a multivariate survival analysis of pancreatic cancer patients, who are known to have a highly unfavorable prognosis among the cancers analyzed, urinary pH was identified as a statistically significant prognostic factor. Additionally, significant differences were observed among the 3 urine pH groups when analyzing patients with pancreatic and breast cancers. No significant correlation was found for patients with NSCLC, possibly owing to the relatively limited number of patients in Group 3 (urine pH≤5.5) compared with Groups 1 and 2. As the potential effectiveness of alkalization therapy has been reported in EGFR-mutant NSCLC [35], the heterogeneity of oncogenic driver mutations and standard treatments such as molecular targeted therapies and immunotherapies should be stratified. For similar reasons of sample size, multivariate survival analysis indicated no significant association between urine pH level and survival among breast cancer and NSCLC patients. In the future, we aim to conduct further stratified analyses with a larger sample size through multicenter collaborative studies.

It has become clear that metabolic abnormalities give cancers unique properties, and that the acidic TME promotes cancer growth and progression, making cancer cells resistant to treatment [10, 11, 36, 37]. It is hence reasonable to propose that alkalizing the TME can reduce the aggressiveness of cancers and enhance the effectiveness of treatments [3].

Systemic alkalization, diet, and metabolic entropy

The human body can be regarded as a dissipative structure, so reducing the system's entropy is possible [12]. Cancer cells may have increased entropy (instability and complexity) owing to metabolic abnormalities and genomic mutations, which increases their treatment resistance. The concept of 'dissipative structure' is attracting attention as a method of reducing this entropy. Dissipative structures refer to the organized patterns of stable structures forming in the flow of matter and energy in nonequilibrium open systems. Multicellular organisms, including humans, are examples of dissipative structures, and controlling the entropy within the body to suppress the growth of cancer cells is expected to be a new means of suppressing the aggressiveness of cancer cells and improving treatment effects.

Biological plausibility of alkalization therapy

One method of reducing systemic entropy is the concept of PRAL, which is a key factor of alkalinization therapy [12, 38–41]. High-protein foods, such as meat and cheese, increase acid production in the body, whereas fruits and vegetables increase alkalinity. A diet with a high PRAL value can cause a state of metabolic acidosis and is associated with the development of metabolic abnormalities, such as insulin resistance, diabetes, hypertension, chronic kidney disease, bone disease, low muscle mass, and other complications.

In clinical practice, our group has demonstrated that improving patients' body constitution and changing their urine pH to alkaline can improve the efficacy of cancer treatment [30]. Previous studies have shown that metabolic acidosis, indicated by a decrease in urine pH, reflects the excretion of excess protons produced in the body [42–44]. As a result of aerobic glycolysis, cancer cells actively extrude protons to sustain an alkaline intracellular pH through proton extrusion mechanisms, including NHE-1 [45]. Notably, NHE-1 activity ceases when the extracellular pH reaches 7.5 [46].

Building on this mechanistic rationale, preclinical studies in mouse models have demonstrated a correlation between intratumoral pH and urinary pH under alkalization therapy, along with improved therapeutic efficacy of chemotherapy. In the Colon26 tumor mouse model, sodium bicarbonate administration enhanced the anti-tumor effect of doxorubicin [47]. Similarly, sodium potassium citrate administration increased the therapeutic effect of TS-1, oral active 5-fluorouracil derivatives, in the Panc-1 pancreatic cancer-xenograft mouse model. Both studies reported an increase in blood HCO_3^- concentration and urine pH following these alkalizing agents. Notably, direct measurement of intratumoral pH confirmed the increase in TME [48]. Therefore, alkalization therapy, by raising the urine pH, may serve as a complementary approach to reducing proton excretion, thereby shifting the internal environment from one that supports cancer growth to one that impairs its survival [31].

Future directions

A comprehensive understanding of the metabolic abnormalities associated with cancer is essential for the development of innovative treatment strategies. Considering that cancer arises and advances owing to metabolic disruptions, it may be feasible to mitigate the onset and progression of cancer through the regulation of the body's pH [49, 50].

Conclusions

This study analyzes the long-term prognosis of cancer patients undergoing alkalization therapy. Our results suggest that urinary pH may be a prognostic indicator for certain types of cancer. In pancreatic cancer, a multivariate survival analysis showed that urinary pH is a statistically significant prognostic factor. For breast cancer patients, categorizing patients by three different urine pH levels revealed significant differences in survival rates. In patients with NSCLC, a cut-off level of pH 5.5 also showed a significant difference in outcomes. However, a key challenge remains in developing an effective method to measure the pH of the TME and establishing a correlation between the alkalization of urine and that of the TME.

We acknowledge several limitations of this study. This investigation was a single-center, retrospective analysis focused on evaluating the safety and efficacy of alkalization therapy. Nonetheless, genetic mutations and concomitant chemotherapy were not adjusted as confounding factors, which renders their associations ambiguous. Moreover, the impact of combination therapies – such as chemotherapy, molecular-targeted therapy, and immunotherapy – on clinical outcomes were not controlled for. Conducting stratified or subgroup analyses could enhance the interpretability of the results. Additionally, while information regarding prior treatments at other institutions was accessible at the time of the initial consultation, data concerning treatments administered after the first visit outside the Wada clinic were collected only partially. Regular and comprehensive follow-up on these variables may be crucial for a more precise assessment of treatment outcomes. Finally, although the findings are promising, the single-institution, non-randomized study design inherently limits the external validity. Future validation through randomized controlled trials or well-structured matched cohort studies will be necessary to substantiate these observations.

Although the mechanism underlying the varying effectiveness of alkalization therapy among different cancer types is not yet fully understood, and the sample size was limited in this study, using urine pH as an indicator for systemic acid-base balance holds promise for enhancing cancer treatment effectiveness and improving patient compliance, as it is a simple and noninvasive test. Further research is needed to investigate the full potential of alkalization therapy and its underlying mechanisms.

Acknowledgments: We would like to formally acknowledge Dr. Kazuyuki Suzuki from the Department of Informatics, The University of Electro-Communications (Tokyo, Japan),

for his invaluable support and expertise in statistical analyses, which substantially contributed to the success of this study.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki, approved by the Institutional Review Board of the Japan Chapter of the American College of Chest Physicians (approval number 2023-1), and has been registered with UMIN Clinical Trials under registration number UMIN000052333 (date of the registration: 21 September 2023).

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

Author contributions: Shion Kachi: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. Reo Hamaguchi: Conceptualization, Supervision, Writing – review & editing. Ryoko Narui: Conceptualization, Supervision, Writing – review & editing. Hiromasa Morikawa: Conceptualization, Data curation, Supervision, Writing – review & editing. Toshihiro Okamoto: Conceptualization, Supervision, Writing – review & editing. HS: Conceptualization, Data curation, Supervision, Writing – review & editing. Hiromi Wada: Conceptualization, Data curation, Supervision, Visualization, Writing – review & editing.

Use of Large Language Models, AI and Machine Learning Tools: None declared.

Conflict of interest: The author states no conflict of interest.

Research funding: None declared.

Data availability: Not applicable.

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