

Alkalinizing the Acidic Tumor Microenvironment Enhances Cancer Treatment Effectiveness

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Introduction

Mitochondria, critical for cellular energy production, contribute to cancer progression by promoting glycolysis even in oxygen-rich conditions, a hallmark of the Warburg effect. This metabolic reprogramming enables cancer cells to maintain an alkaline intracellular pH and the acidic Tumor Microenvironment (TME), fostering tumor growth, immune evasion and therapy resistance.

Alkalinization therapy, primarily through dietary interventions, neutralizes the acidic TME to enhance cancer treatment efficacy. By consuming low Potential Renal Acid Load (PRAL) foods and alkalizing agents, systemic acidity is reduced, with urine pH serving as a practical biomarker.

Data from the Wada Clinic indicate significantly improved five-year survival rates for stage IV cancers. Notably, patients with non-small cell lung cancer exhibited a five-year survival rate nearly eight times higher than that reported by the National Cancer Center Japan. These findings suggest that incorporating pH modulation into cancer treatment represents a substantial advancement, providing a complementary approach and exploring new avenues for advanced-stage cancers.

The Tumor Microenvironment (TME) is acidic, a characteristic closely linked to the metabolism of cancer cells. In the 1920s, Otto Warburg discovered that tumor tissues metabolize approximately ten times more glucose into lactate than normal tissues, a phenomenon now known as the Warburg effect [1-5]. The Warburg effect is characterized by cancer cells generating much of their energy through glycolysis, even in sufficient oxygen. Many cancer cells shift their metabolism toward glycolysis while maintaining minimal levels of mitochondrial respiration. This metabolic trait is also suggested by the studies of Goldblatt and Cameron on oxygen deprivation and tissue culture. They discovered that intermittent oxygen deprivation promotes the formation of cancer cells and proposed that cancer

development is triggered in environments rich in nutrients but deficient in oxygen [6].

Description

Generally, oxygen deprivation leads to mitochondrial disruption within cells, inducing apoptosis [7-9]. However, some cells exposed to such conditions activate a 'retrograde response' as a metabolic adaptation to hypoxia [10], allowing them to survive by relying on glycolysis [11-13].

Cancer cells exhibit unique metabolic characteristics contributing to their aggressiveness and treatment resistance. One such feature is the shift toward an alkaline intracellular pH (pHi) and the acidification of the TME [14]. In normal cells, intracellular pH is regulated by balancing proton influx and efflux through proton pumps such as the Na⁺/H⁺ Exchanger (NHE-1) [15], maintaining a slightly acidic or neutral pH. In contrast, cancer cells expel excess protons produced during glycolysis and overexpress NHE-1 transporters, maintaining an alkaline intracellular environment (pHi 7.2–7.7) while acidifying the TME [16]. In the acidic TME, cancer cells demonstrate increased motility and invasive capabilities [17]. This state promotes cellular proliferation and division, genetic abnormalities, oncogene expression, enhanced glycolytic activity, DNA synthesis, angiogenesis, metastatic potential and the acquisition of multidrug resistance in cancer cells [18-22].

The acidic TME enables immune evasion of cancer cells by suppressing the tumor immune response. The extracellular acidic environment induces the recruitment and accumulation of Myeloid-Derived Suppressor Cells (MDSCs) within the TME. Furthermore, killer T-cell activation is inhibited, regulatory T cells accumulate and the secretion of IFN-γ and TNF-α is reduced. This environment also weakens the antitumor activity of natural killer and dendritic cells [23-28].

An increase in intracellular pH (pHi), or alkalization, within cancer cells has been shown to reduce the intracellular uptake

of chemotherapeutic agents such as adriamycin, vinblastine and cisplatin [15,29]. Notably, research suggests that increasing the pHi from 7 to 7.4 can enhance resistance to adriamycin in human lung cancer cells by up to 2000-fold [30]. Alkalization therapy is a concept aimed at neutralizing the acidic TME, lowering cancer cells intracellular pH and inducing apoptosis. This approach has the potential to enhance cancer treatment efficacy and provides the following advantages [31,32].

- Suppression of tumor cell proliferation and metastatic ability.
- Overcoming multidrug resistance and enhancing the effectiveness of chemotherapy and immunotherapy.
- Restoration of killer T-cell and natural killer cell activity.
- Remodeling of the tumor microenvironment by suppressing the production of inflammatory cytokines.
- Metabolic reprogramming by reducing the dependence of cancer cells on glycolysis.

Alkalization therapy can overcome resistance mechanisms by targeting pH imbalances, rendering cancer cells more vulnerable to treatment. Additionally, alkalizing the TME may inhibit proton transporters like NHE-1, which play a crucial role in maintaining the alkaline intracellular environment that supports cancer cell survival and proliferation.

The alkalization therapy practiced at the wada clinic involves consuming alkalinizing diets and bicarbonate-citric acid preparations. Specifically, this includes the intake of bicarbonates, increasing the consumption of vegetables and fruits and reducing the intake of meat and processed foods. This approach is based on the PRAL (Potential Renal Acid Load for Kidney Disease) index [33], indicating foods' acidity or alkalinity. We recommend increasing the intake of fruits and vegetables

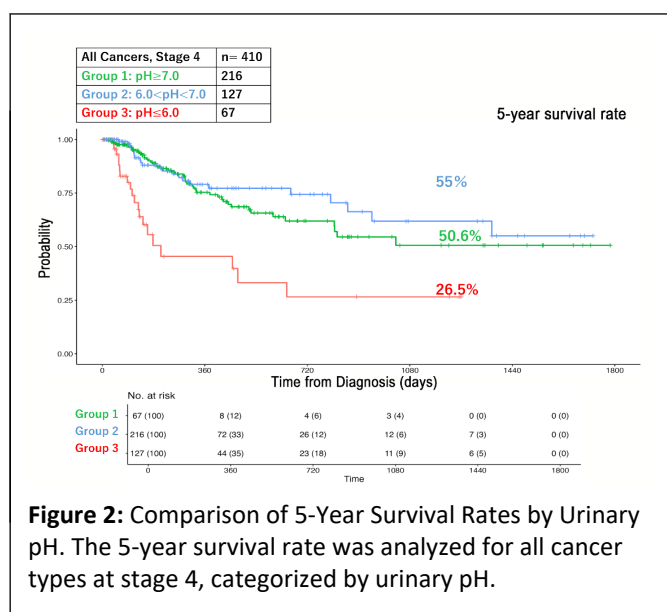
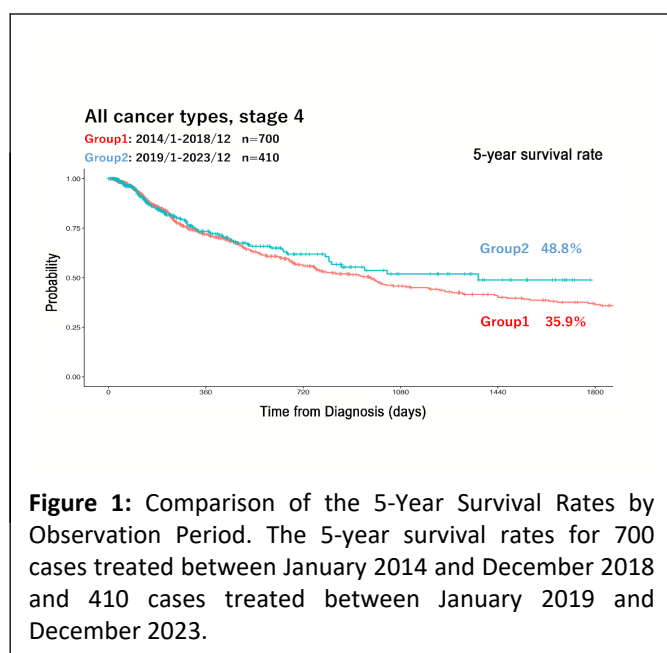
with low PRAL values, which promote alkalization, while limiting the consumption of high-PRAL foods such as animal proteins, processed foods and sugary items. Although directly measuring the acid-base balance of the TME in clinical settings is challenging, urinary pH can be used as an indirect marker. We have demonstrated favorable treatment outcomes, including improved survival prognosis and enhanced efficacy of existing chemotherapies, in cases of malignant lymphoma, gastric cancer, small cell lung cancer and breast cancer, where urinary pH alkalization was achieved [34-38].

The results of observational studies conducted over the past decade are summarized below. From January 2014 to December 2023, approximately 4,500 cases were treated at our clinic, of which 1,414 cases involved stage IV cancers across all cancer types. Among these, various analyses were conducted on 1,110 evaluable cases. Table 1 illustrates that the 5-year survival rate for stage IV cancers at the Wada Clinic was 37.7%. In contrast, the National Cancer Center Japan reported a 5-year survival rate of just 15.7% for the same time period [39], resulting in a difference of 22%. Moreover, as depicted in Figure 1, the 5-year survival rates for 700 cases treated between January 2014 and December 2018 and 410 cases treated between January 2019 and December 2023 were 35.9% and 48.8%, respectively, showing improved outcomes in the most recent 5 years. This improvement can be attributed to the accumulation of operational experience with alkalization therapy. Figure 2 compares 5-year survival rates by urinary pH. Cases with a pH > 7 had a 5-year survival rate of 50.6% (n=216), those with 6 < pH < 7 had a rate of 55% (n=127) and cases with pH ≤ 6.0 had a significantly lower rate of 26.5% (n=67).

Table 1: Comparison of data from the Wada Clinic and the Japan National Cancer Center.

	Patients of the Wada Clinic (n)	The 5YSR of the Wada clinic (%)	5YSR of the National Cancer Center (%)
All cancers	1110	37.7%	15.7%
Pancreatic Cancer	127	7.9%	1.8%
Breast Cancer	131	44.3%	39.3%
NSCLC	253	48.6%	6.4%

Note: The 5-year survival rate for stage 4 cancer was compared and examined using data from the Wada Clinic and the National Cancer Center. The total number of cases at the Wada Clinic for all types of cancer was n=1110, with 127 cases of pancreatic cancer, 131 cases of breast cancer and 253 cases of non-small cell lung cancer. The Wada Clinic carries out alkalization therapy for all types of cancer and compared to the data from the National Cancer Centre, the data showed an improvement of around 6-42%.



Neutralizing the acidic TME has emerged as a promising new strategy in cancer treatment. Alkalinization therapy can potentially improve treatment outcomes by suppressing tumor malignancy and restoring immune responses. While further research is necessary, this approach holds the potential to revolutionize cancer therapy, particularly when combined with chemotherapy or immunotherapy, offering the possibility of significantly improving patient prognosis.

Mitochondria are essential organelles in eukaryotic cells, responsible for energy production *via* Oxidative Phosphorylation (OXPHOS) [40]. Under hypoxic conditions, mitochondria cannot sustain energy production through OXPHOS and instead activate apoptosis, playing a critical role in maintaining tissue homeostasis.

Recent studies have revealed that mitochondrial dysfunction and alterations in energy metabolism are central to

tumorigenesis. Specifically, signaling through "retrograde responses" from mitochondria to the nucleus induces metabolic changes, enabling cells to survive under hypoxic conditions [41-44]. This adaptation ultimately results in cancer cells that continue to produce energy through glycolysis even in the presence of oxygen, a phenomenon fundamental to the "Warburg effect".

Therefore, mitochondria play a crucial role in cancer development and progression. Their involvement in energy metabolism, apoptosis regulation and cellular adaptation to hypoxia underscores their importance in tumor biology. Understanding these mechanisms could provide valuable insights into potential therapeutic strategies targeting mitochondrial dysfunction in cancer treatment.

Detoxification within the body is considered crucial for enhancing the effectiveness of cancer treatment and reducing the aggressiveness of cancer cells. A key concept in this detoxification process is the idea of dissipative structures [45]. Dissipative structures, also referred to as 'nonequilibrium open systems,' describe the mechanism by which order emerges in living organisms, maintained by the metabolism of energy supplied from the external environment. In general, an increase in entropy, the degree of disorder, within the body can lead to disease. However, dissipative structures could decrease entropy. According to the second law of thermodynamics, entropy in an isolated system always increases. However, entropy reduction through 'reversible processes' becomes possible in nonequilibrium open systems, where energy and matter are exchanged with the environment. This mechanism allows the system to decrease overall entropy and restore order within the body under conditions of appropriate external energy supply [46]. Specifically, the human body utilizes external energy sources such as food and oxygen to maintain order. However, improper intake methods can disrupt this internal order. From this perspective, understanding the concept of dissipative structures and applying it to cancer treatment offers a novel approach to inhibiting cancer progression and provides a fresh viewpoint in therapeutic strategies.

In this context, alkalinization therapy, by correcting imbalances in the body's pH, holds the potential to suppress cancer activity and synergistically enhance the efficacy of existing cancer treatments.

Conclusion

Observational studies at the Wada Clinic have demonstrated that implementing alkalinization therapy through oral administration, with urinary pH as a biomarker, is associated with favorable survival outcomes in stage IV cancer patients. This approach embodies the principles of 'Science-Based Medicine' (SBM), which relies on inductive reasoning and validation based on individual cases and scientific data rather than the deductive reasoning of traditional evidence-based medicine (EBM), which draws on prior validated results.

Alkalinization therapy was developed through this inductive process, focusing on the observed correlations between pH regulation, cancer progression and the clinical outcomes of

patients undergoing this therapy. By challenging and complementing the methodologies of EBM, SBM integrates innovative treatments like alkalization therapy, offering new hope for patients with complex cancers. Alkalization therapy highlights the significance of metabolic and environmental factors in cancer causation, providing a holistic approach that complements conventional therapies. This integrative strategy not only aims to inhibit cancer progression but also to enhance the effectiveness of existing treatments, fostering a broader paradigm for cancer care.

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Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could potentially create a conflict of interest.

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