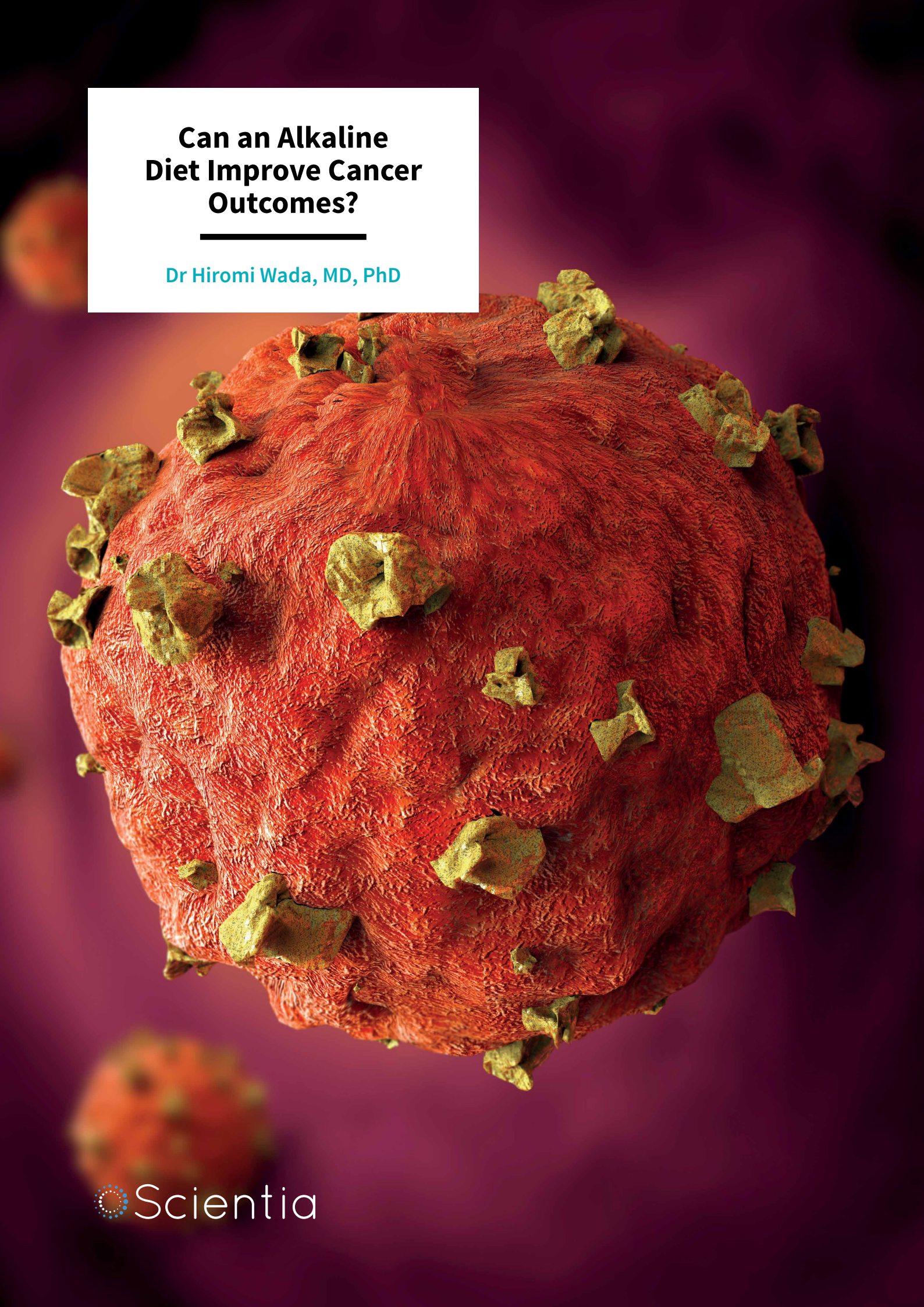
Can an Alkaline Diet Improve Cancer Outcomes?

Dr Hiromi Wada, MD, PhD



Scientia

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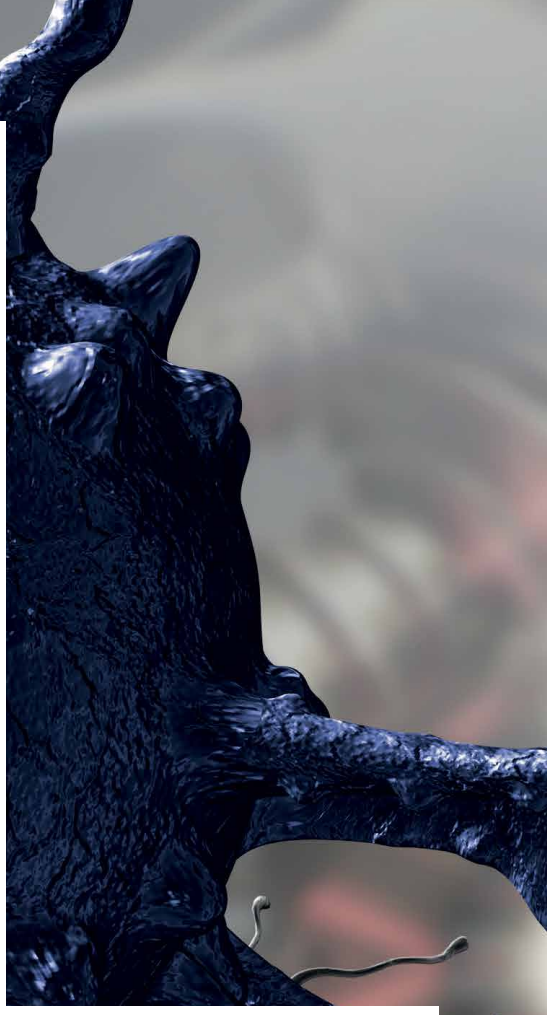
There is a strong body of evidence from animal and human studies showing that the acidic external microenvironment (local environment) of cells associated with tumours plays a significant role in the progression and migration of cancers. Indeed, in a rat model, systemic buffering which reduces acidic pH levels also reduces both cancer progression and drug resistance. **Dr Hiromi Wada** at the Japanese Society of Inflammation and Metabolism in Cancer and his colleagues are investigating the effect of an alkaline diet on the tumour microenvironment, and its potential to enhance the efficacy of anti-cancer treatments.



The Impact of Diet

It has been proposed that an alkaline diet may bring benefits to the conventional treatment of cancer, based on its ability to modify the pH of the tumour microenvironment. Alkaline foods include fruit, vegetables, legumes, nuts, and seeds. However, there is currently a lack of robust clinical evidence demonstrating a relationship between diet and cancer development and progression.

More specifically, prospective cohort studies in which groups of individuals have been observed over periods of time have failed to demonstrate an association between the dietary consumption of fruit and vegetables and the prevention of cancer. However, observational case control studies have suggested some interesting associations. These discrepancies in findings may be due to methodological differences and confounding variables among studies, such as the insufficient follow up of patients.

An Alkaline Diet and Advanced Non-small Cell Lung Cancer (NSCLC)

To better understand the relationship between an alkaline diet and cancer, Dr Hiromi Wada at the Japanese Society of Inflammation and Metabolism in Cancer and colleagues conducted a retrospective assessment of eleven patients diagnosed with either advanced stage or recurrent NSCLC with an epidermal growth factor receptor (EGFR) mutation – that is, a DNA mutation in the genes that code for this protein which is important in cell division and survival.

The patients had been treated with tyrosine kinase inhibitor (TKI), a protein which targets the mutated EGF-receptor and had also been directed to consume a diet rich in alkaline foods.

The compliance of patients with an alkaline diet was confirmed by urine pH analysis. The team found, in some cases, the TKI treatment was reduced to almost half of the standard treatment dosage (Figure 1). When compared to similar studies, the resulting progression-free survival (PFS; defined as the length of time during and after treatment that a patient still has the disease but without worsening) increased from 13 months to 19 months. Furthermore, overall survival increased from 22.8 months to 28.5 months.

While Dr Wada and his colleagues acknowledge that there was no direct comparator group in this study, the findings when considered with the existing literature support their important proposal that combining an alkaline diet with a lower dose of EGFR-TKI treatment may reduce the toxic side effects of the treatment while extending the PFS of the patients.

Alkalisation Therapy and Stage IV Metastatic or Recurrent Pancreatic Cancer

Pancreatic cancer is highly aggressive and associated with extremely poor outcomes even when treated with combined chemotherapy regimens. In another clinical trial, Dr Wada and his colleagues supplemented chemotherapy treatment of advanced

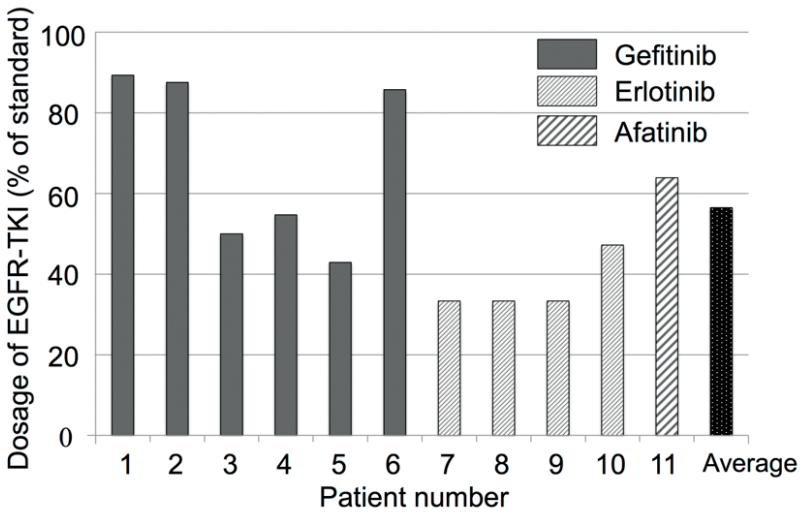


Figure 1. Dosage of EGFR-TKI (from Anticancer Research, 2017, 37, 5141–45).

pancreatic cancers by prescribing an alkaline diet, comprising of a minimum of 400 grams per day of fruits and vegetables along with a total exclusion of meat and dairy, and daily consumption of an oral sodium bicarbonate solution. The study outcomes, measured in 28 participating patients, were urine pH and mortality.

Following alkalisation therapy, mean urine pH was significantly higher than at the initiation of the trial, and the research team found that patients with higher urine pH (i.e., being more alkaline) had a higher overall survival (OS) rate than those with lower (more acidic) urine pH. These patients had an OS rate of 16.1 months compared to only 4.7 months for patients with more acidic urine (Figure 2A). Similarly, the patients who had a greater difference in urine pH (>1) from pre- to post-alkalisation therapy also had a greater OS. In these cases, the OS was 16.1 months compared to 4.3 (Figure 2B).

Intra- and Extra-cellular pH: Effects on Tumour Physiology and Pathology

In general, cancer cells exhibit a shift towards alkalinity in the intracellular environment. In other words, the cytoplasm within the cancer cells is alkaline (pH>7) and the corresponding extracellular environment is acidic.

Alkalisation within the cancer cells is pivotal to the initiation of malignancy and the progression of the tumour, with some researchers reporting associations with key tumour processes, including the induction of multi-drug resistance and the inhibition of programmed cell death (apoptosis).

The Sodium/Hydrogen Transporter (Isoform 1) NHE1

NHE1 is responsible for maintaining the acid/alkali balance within normal cells. With a typical ('set point') level of 6.9–7.1, this transporter is largely inactive in the steady state. However, in transformed cells, the NHE1 transporter has an altered set point and remains active in the pH 7.2–7.7 range. Consequently, this leads to an alkaline environment within the cells and an acidic environment immediately surrounding the cells.

The theory of alkalisation is based on altering the pH of the environment surrounding the tumour cells, such that increasing the pH of the acidic surrounds to be close to that of the inside of the tumour cells (pH 7.2–7.7) prevents the transport action of NHE1 and prevents the self-driven proliferation of cancer cells.

NHE1: Tumour Proliferation and Metastasis

Other researchers have confirmed the association between NHE1, tumour proliferation, and increased internal cellular pH by blocking either cell proliferation or the action of the transporter and determining the intracellular pH.

Furthermore, the alkaline internal environment which results from the action of the NHE1 transporter promotes the production of factors which, in turn, induce angiogenesis, the formation of new blood vessels that is necessary for the dissemination of metastatic tumours. Furthermore, the acidic external pH promotes the actions of a number of factors that support the proliferation and mobilisation of tumour cells.

One of the most significant aspects of the action of NHE1 is that it does not require any growth factor to stimulate its action. This means that a change in intercellular pH is all that is required to induce the conditions that lead to cell proliferation.

Alkalisation and the Effect on Cancer Immunotherapies

In addition to chemotherapies, antibody therapies are also used as therapies in some cancer treatments. A treatment for esophagogastric junction adenocarcinoma, Nivolumab, was used in conjunction with alkalisation in one elderly patient. Dr Wada and colleagues reported positive findings in this case study, where the patient consumed an alkaline diet in combination with oral sodium bicarbonate. They showed that tumour markers reverted to normal levels from extremely high values prior to treatment, and furthermore, a computerised tomography scan at 12 months post-treatment identified shrinkage of the esophagogastric junction tumour and the liver metastases.

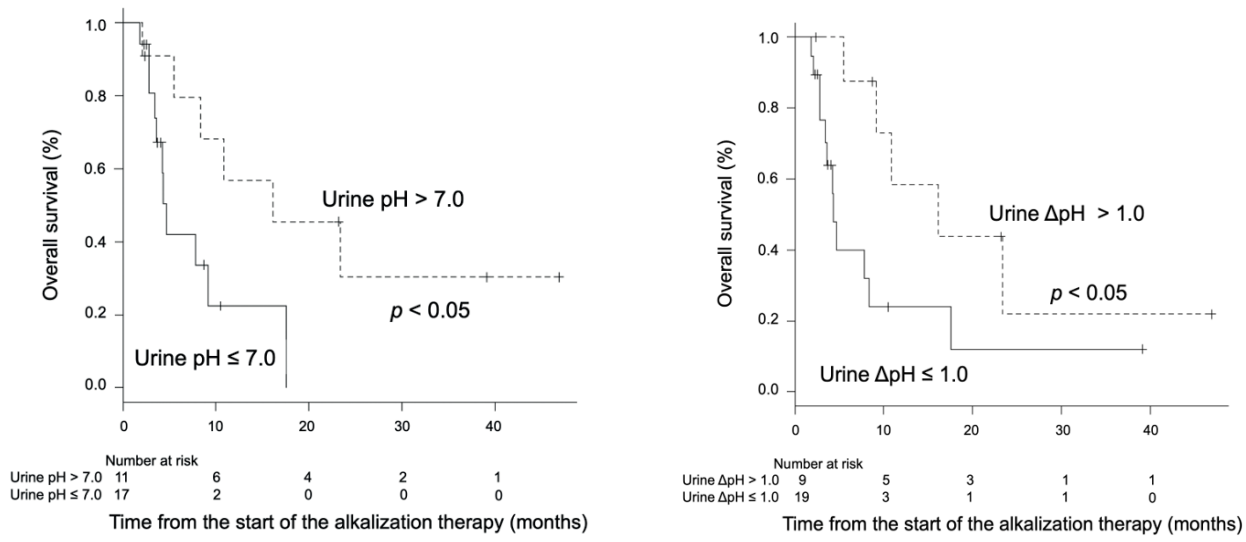


Figure 2. Association between overall survival of advanced pancreatic cancer patients and urine pH (A) or urine ΔpH (B) (from Anticancer Research, 2020, 40, 873–80').

Dr Wada and his group note that this case study, the first of its kind, highlights the potential correlation between alkalinisation of the tumour microenvironment and positive outcomes from antibody therapy in cases that have shown no benefit from multiple other therapies.

Chemotherapy Resistance and Diet

It is known that the internal (cytoplasmic) pH of most cancers is alkaline, and some researchers have shown that this is a central aspect of chemotherapy resistance. Specifically, in alkaline environments, some chemotherapy drugs are shown to be present within the tumour cells at lower concentrations in alkaline conditions than in acidic (lower pH) conditions.

This means that when NHE1 is active and the intercellular pH increases, chemotherapy treatments are substantially less effective, and the tumour cells become resistant to the actions of the drugs. As all of the cancer cells are not killed by the treatment – common in most situations – the internal pH of the remaining cells increases further and the cells become more resistant to the drugs. The drugs cannot induce apoptosis and the tumour advances.

In some tests using cultured cell lines, the resistance to key chemotherapy drugs has been shown to increase almost 2000-fold in response to an increased intercellular pH of 0.44.

Dr Wada and colleagues argue that the beneficial results they have observed in patients with aggressive, late stage cancers that frequently become resistant to chemotherapy support their concept that alkalisation of the tumour microenvironment through the manipulation of diet and consumption of oral sodium bicarbonate solution leads to a reduced pH in the internal cellular environment. Ultimately, this manipulation of the pH in the local tumour environment may increase the sensitivity of the tumour cells to chemotherapeutic agents.

The Future

Dr Wada and colleagues discuss the limitations of their work to date, necessitated by the nature of treating late-stage cancers. However, their findings associated with alkalisation (achieved through diet and, in some cases, supplementation with oral sodium bicarbonate) in patients with late stage or metastatic tumours indicate improved patient outcomes. These include OS, PFS, tumour and metastatic reduction, and improved sensitivity of the tumours to chemotherapeutic and antibody-based drugs. In one case, Dr Wada and his team even report improved outcomes with alkalisation therapy in a patient with a multi-drug resistant tumour.

In addition to their impressive clinical findings, Dr Wada and his team present a clear mechanism for the pathology and physiology of cancers in association with an acidic external and alkaline intracellular environment, thus demonstrating how the pH balance leads to cellular proliferation, angiogenesis, and formation of metastatic tumours.

Dr Wada and his team are also interested in the area of mental well being and cancer development and progression, advocating that suppressing overactivation of the hypothalamic-pituitary-axis, the body's central stress response system, prior to cancer treatment brings tangible benefits to the patient. One's emotions have a direct effect on the pituitary, which leads to the production of stress-associated hormones, disrupting the body's hormones and dampening the immune response. As such, Dr Wada also advocates a treatment approach aiming to minimise stress and enhance the benefits of cancer interventions.

Meet the researchers

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Dr Hiromi Wada graduated from the Faculty of Medicine at Kyoto University, Japan, as a Doctor of Medicine. He then worked at the Institute for Chest Disease Research and Institute for Frontier Medical Sciences at Kyoto University before becoming a Professor in the Department of Thoracic Surgery, which is also at Kyoto University. Dr Wada is currently a Professor Emeritus at Kyoto University, Director of the Karasuma Wada Clinic, and Representative Director of the Japanese Society of Inflammation and Metabolism in Cancer.

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Dr Hiromasa Morikawa received his MD in 2001 from the School of Medicine at Kyoto University, Japan. After working as a thoracic surgeon, he received a PhD for his research on T-cell immunology conducted at Dr Shimon Sakaguchi's laboratory. After working as an Assistant Professor there, he moved to Karolinska Institutet in Sweden, working in computational medicine and immunology at Dr Jesper Tegner's laboratory as a Vinnmer-Marie Curie Fellow. He is currently working at Karasuma Wada Clinic in Japan and is a Board Member of the Japanese Association for Chest Surgery.

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Dr Reo Hamaguchi graduated from Kanazawa University School of Medicine and is currently undertaking graduate studies at Tokyo University School of Medicine. He is a Certified Internist at the Japanese Society of Internal Medicine, a Specialist in Chest Medicine, and a Certified Oncologist. Dr Hamaguchi is also the Chief Physician at the Mirai Medical Clinic in Myogadani, Tokyo. Over his career, he has worked as a pulmonologist in the treatment of patients with general internal medicine diseases as well as cancer. He currently studies under the supervision of Dr Wada, and treats cancer patients through the improvement of diet and the enhancement of immunity in consideration of the inflammation and metabolism of cancers.

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Dr Ryoko Narui graduated from Kobe University School of Medicine and is a Board Certified Surgeon at the Japan Surgical Society. After working as a surgeon in general surgical disease as well as gastrointestinal cancer and breast cancer, Dr Narui completed a Fellowship in Integrative Medicine at the University of Arizona, Center of Integrative Medicine, led by Dr Andrew Weil. She received a scholarship from CWAJ and completed a master's degree in Medical Humanities at King's College, London. She currently studies under the supervision of Dr Wada.

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