News Release

## Title

Preclinical verification of the efficacy and safety of aqueous plasma for ovarian cancer therapy

## Key Points

- Plasma-activated medium (PAM) showed a metastasis-inhibitory effect on ovarian cancer through a PAM-evoked immune response.
- Intraperitoneal washing with plasma-activated lactate Ringer's solution (PAL) significantly improved the overall survival rate in an ovarian cancer mouse model.
- Intraperitoneal washing therapy with aqueous plasma might be effective to improve clinical outcomes of early stage ovarian cancer.

## Summary

This work is mainly from the team of Hiroaki Kajiyama (Professor, Department of Obstetrics and Gynecology) and Nobuhisa Yoshikawa (Assistant Professor, Department of Obstetrics and Gynecology) in Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.), in collaboration with the team of Masaaki Mizuno (Professor, Center for Advanced Medicine and Clinical Research) in Nagoya University Hospital (Director: Yasuhiro Kodera, M.D., Ph.D.) and Masaru Hori (Director, Center for Low-temperature Plasma Sciences) and their team members. We demonstrated new insights into a metastasis-inhibitory effect of the plasma-activated solutions in ovarian cancer cells in vivo and developed a new approach to treat ovarian cancer in clinical practice. There have been many reports showing the effect of plasma-activated solutions on cell death of ovarian, gastric, pancreatic cancers, and glioblastoma brain tumor cells in Nagoya University. In this study, we found that the plasma-activated solution inhibited intraperitoneal microdissemination which is difficult to assess by gross pathology, through involving of macrophages, one of the immune cells. Moreover, intraperitoneal washing therapy with the plasma-activated solution significantly improved the overall survival rate in an ovarian cancer mouse model without severe adverse effects. Our results suggest that the aqueous plasma washing therapy might have the potential of preventing the recurrence of ovarian cancer patients who are diagnosed with early stage. The paper was published in the journal of *Cancers* on Mar. 7th, 2021, and DOI is doi: 10.3390/cancers13051141.

## Research Background

Ovarian cancer is one of the most lethal gynecological malignant diseases. Patients with ovarian cancer are diagnosed at an advanced stage because of its asymptomatic progression, accompanied by metastasis in the peritoneal cavity. The current treatment for advanced ovarian cancer patients is debulking surgery followed by a combination of paclitaxel +

platinum chemotherapy. Since rapid metastasis to the peritoneum, the patients have a poor prognosis with the present treatments and the 5-year survival rate is less than 50%. Non-thermal plasma has been focused on as a novel medical practice. Some of the plasma medical devices for the sterilization of skin and oral were already in practical use. Recently, clinical trials for cancer therapy with plasma have been in progress in western countries. At Nagoya University, we have been promoting research towards the creation of plasma medical science and its clinical applications. However, only a few reports have demonstrated the therapeutic effect of plasma which can be actually used in clinical practice and the underlying mechanisms have not been fully elucidated. In this study, we addressed to develop the foundation of plasma clinical application for safety and efficacy.

## Research Results

PAM inhibited the cell viability of various types of ovarian cancer cells in a storage period- and cell number-dependent manner, showing that each cell line had different sensitivity to PAM. Furthermore, this antitumor effect of PAM was antagonized by Iron chelator, deferoxamine on ovarian cancer cells as well as a normal cell. Intracellular catalytic ferrous iron may be one of the key factors to facilitate the antitumor effect of PAM. Moreover, we studied PAM's inhibition of microdissemination onto the omentum by performing in vivo imaging and revealed that intraperitoneal PAM injection treatment markedly suppressed the metastasis on the omentum compared to the controls without severe damage in the mouse body. We further investigated a sequential histological analysis on microdisseminated omentum lesions. The results showed that PAM induced macrophage infiltration into the disseminated lesion. The iNOS-positive signal was co-localized at the macrophages in the existing lesion, indicating that PAM might induce M1-type macrophages in the disseminated site. To apply a new cancer treatment using a plasma-activated solution in a clinical setting, intraperitoneal lavage with PAL was investigated and revealed that a single dose of PAL-washing significantly improved the overall survival rate in an ovarian cancer mouse model.

## Research Summary and Future Perspective

We demonstrated the antimetastatic activity of PAM in the animal model which may reflect the early stage of ovarian cancer. We identified a new mechanism of the antitumor effect through a PAM-evoked immune response. The results may help to predict its benefit for clinical treatment, such as intraabdominal washing treatment for the case with positive ascites cytology in early stage ovarian cancer. To clarify the availability of plasma-activated solutions, further studies should be conducted to achieve additional efficiency and safety for clinical application.

## Publication

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