News Release

Title

Significance of platinum distribution to predict platinum resistance in ovarian cancer after platinum treatment in neoadjuvant chemotherapy

Key Points

- **Platinum-resistant recurrence is important point in ovarian cancer treatment. In clinical settings, it is defined that recurrence within 6 months after the last dose of platinum-based chemotherapy. "Platinum resistance" can be diagnosed only after tumor growth.**
- **LA-ICP-MS clearly revealed the platinum distribution in samples with platinum-based chemotherapy before operation from patients with ovarian cancer**
- **there are two characteristic patterns of platinum distribution that indicate platinum resistance and prognosis prior to recurrence**

Summary

Most patients with ovarian cancer experience recurrence and develop resistance to platinum-based agents. The diagnosis of platinum resistance based on the platinum-free interval is not always accurate and timely in clinical settings. Herein, we used laser ablation inductively coupled plasma mass spectrometry to visualize the platinum distribution in the ovarian cancer tissues at the time of interval debulking surgery after neoadjuvant chemotherapy in 27 patients with advanced high-grade serous ovarian cancer. Two distinct patterns of platinum distribution were observed. Type A (n=16): platinum accumulation at the adjacent stroma but little in the tumor; type B (n=11): even distribution of platinum throughout the tumor and adjacent stroma. The type A patients treated post-surgery with platinum-based adjuvant chemotherapy significantly shorter periods of recurrence after the last platinum-based chemotherapy session ($p=0.020$) and were diagnosed with "platinum-resistant recurrence." Moreover, type A was significantly correlated with worse prognosis ($p=0.031$). Post-surgery treatment with non-platinum-based chemotherapy could be effective for the patients classified as type A. Our findings indicate that the platinum resistance can be predicted prior to recurrence, based on the platinum distribution; this could contribute to the selection of more appropriate adjuvant chemotherapy, which may lead to improves prognoses.

Research Background

Approximately 70% of ovarian cancer cases are diagnosed at an advanced stage with peritoneal dissemination. Neoadjuvant chemotherapy followed by surgery is alternative treatment strategy. Most ovarian cancer are sensitive to initial platinum-based agents, however, nearly 80% of the patients experience recurrence and become resistant to platinum-based agents, which is related to poor long-term survival.

In clinical settings, recurrence within 6 months after the last dose of platinum-based chemotherapy is referred to "platinum-resistant recurrence." The problem is that it allows for the diagnosis of platinum resistance only at the time of tumor growth. Novel biomarkers of platinum resistance are needed so that more appropriate drugs can be used for ovarian cancer earlier in adjuvant treatment, which could prolong the patients' survival and minimize adverse effects caused by platinum-based agents.

The intracellular platinum concentration has been reported to be correlated with some cancer cell lines. Inductively coupled plasma mass spectrometry (ICP-MS) can detect the platinum concentration in dissociated cells with the use of nitric acid. It has not been possible to distinguish between the platinum distributions in a tumor and the platinum distribution in adjacent stroma, but we speculated that the recently introduced method of laser ablation ICP-MS (LA-ICP-MS), which uses a focused laser ablation system combined with ICP-MS (**Fig. 1**), may be useful for distinguishing these platinum distributions. LA-ICP-MS is used to identify the distribution of trace elements in tissue, and a few investigations using LA-ICP-MS have identified the platinum in cancer patients in whom platinum-based agents had been used. We conducted the present study to investigate the usefulness of performing LA-ICP-MS to identify platinum distribution to predict of platinum resistance and cancer prognosis.

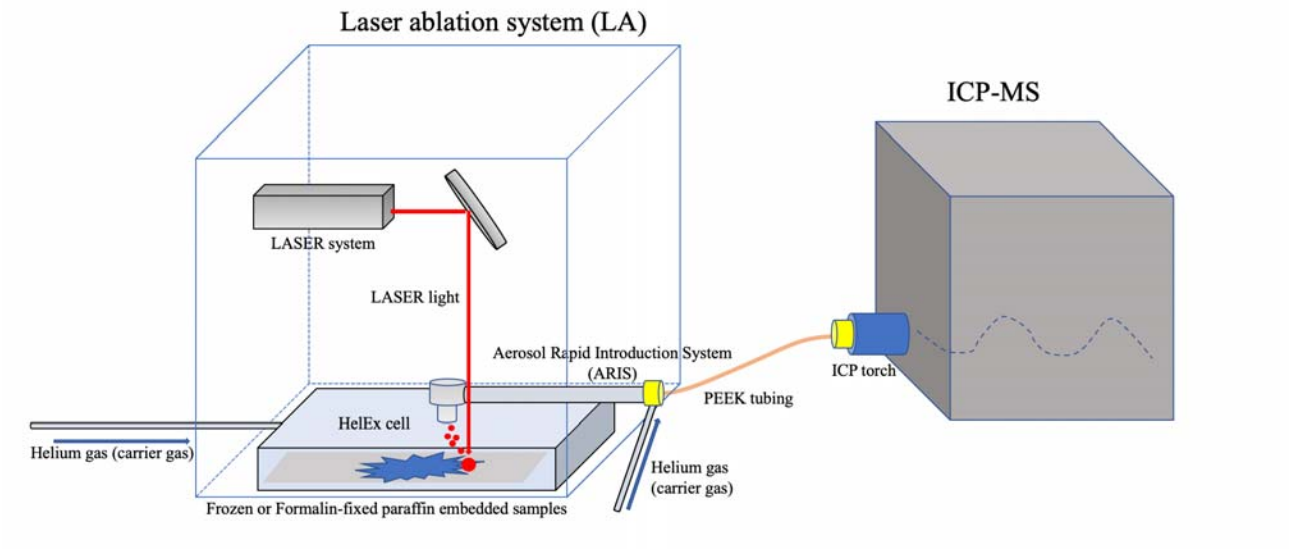


Figure1. Representative LA-ICP-MS image. Samples inserted into a HelEx cell box are ablated by the focused laser. The ablated samples are carried through the aerosol rapit introduction system (ARIS) to the ICP-MS.

Research Results

We firstly evaluated clinically platinum-resistant recurrent ovarian cancer tissues. This patient was treated platinum-based agents. However, her recurrent tumor had shown no response to platinum-based treatment, therefore we resected the solitary tumor. Platinum was not detected in the tumor area but had accumulated in the adjacent stroma (Fig. 2). We hypothesized that true platinum sensitivity can be diagnosed by platinum distribution at the tumor margins before recurrence.

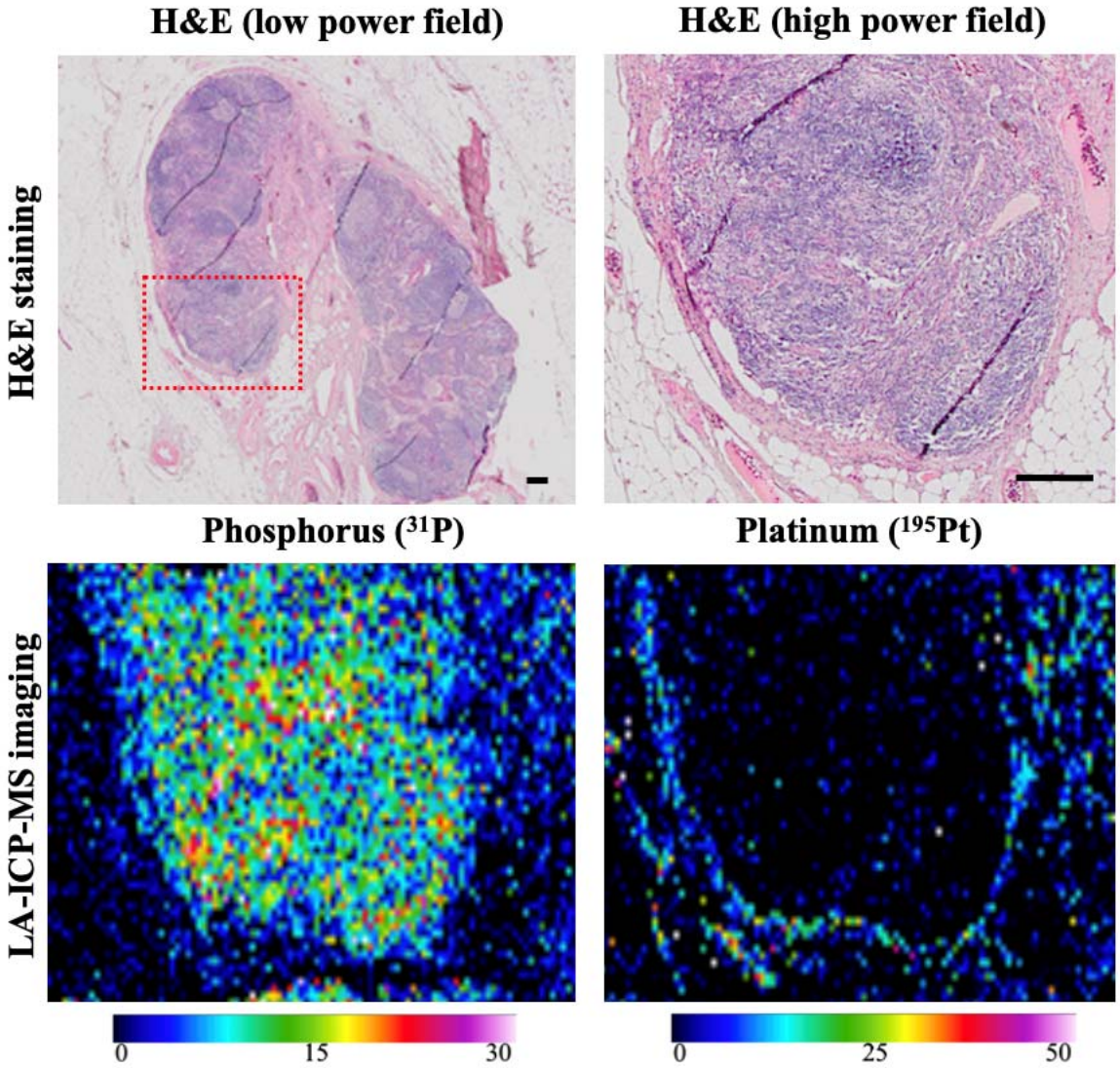


Figure 2. Platinum was not present in the tumor but had accumulated in the borderline area of the tumor and stroma. Scale bar: 200 μm.

We then analyzed the samples which were treated with platinum regimens before operation. A total of 27 samples were analyzed. We have classified these patients into two groups according to the distribution of platinum by LA-ICP-MS. Type A refers to specimens with low platinum counts in the tumor but with the high platinum counts in the adjacent stroma, whereas type B refers to specimens with the comparable platinum counts both in the tumor and adjacent stroma (Figure 3A and 3B). Of the 27 cases, 16 were classified into type A

and the other 11 were type B. In terms of recurrence, none of the type B patients in type B experienced recurrence within 6 months from the last platinum-based drug. Conversely, nine of the 16 (56.3%) type A patients experienced recurrence within 6 months. It identified a significantly difference between the type A and B in only patients who were treated post-surgery with platinum-based agents (Figure. 3C, p=0.020).

With respect to OS, all but one of the 11 type B patients lived for >3 years after diagnosis, whereas eight of the 16 type A patients died within 3 years after diagnosis, demonstrating that the type A patients had a significantly worse prognoses (Fig. 3D, p=0.031).

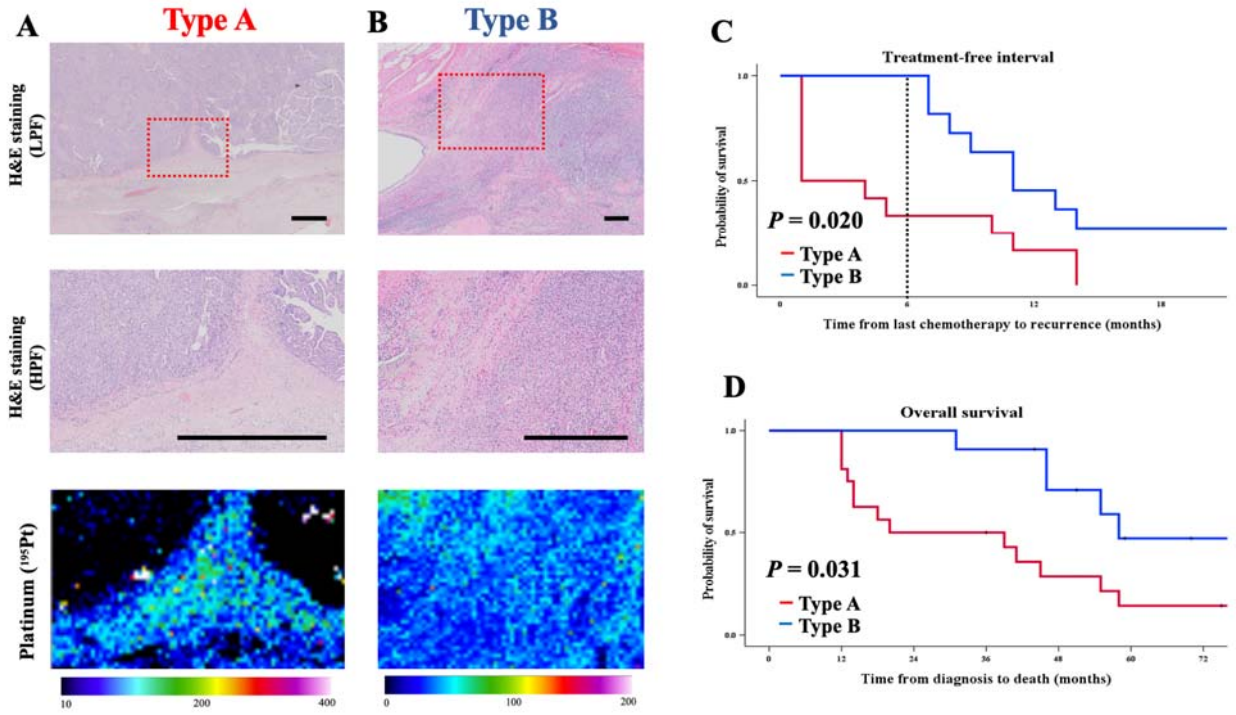
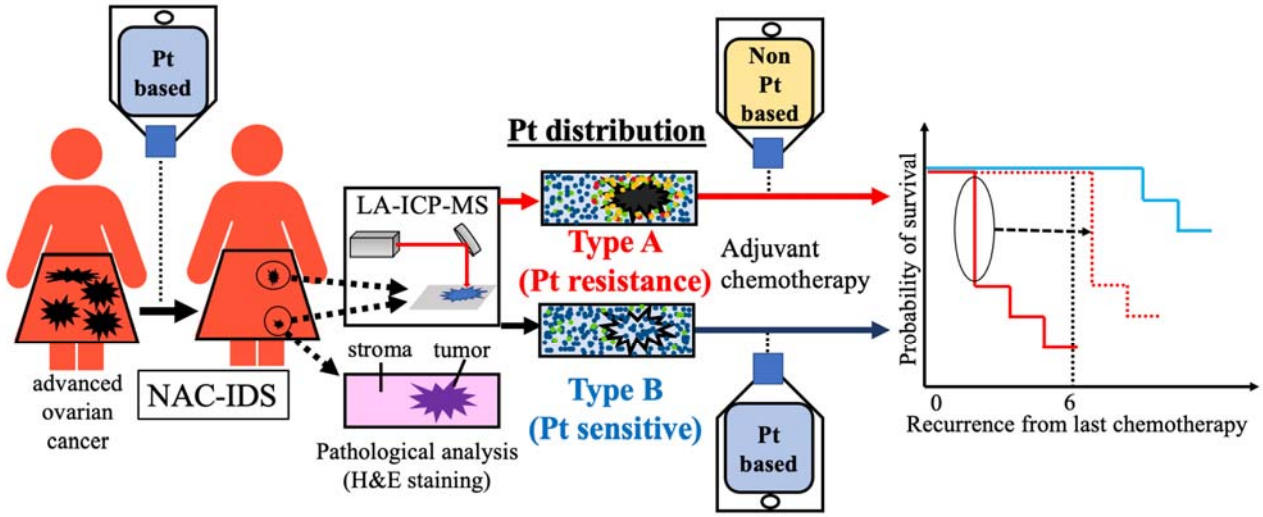


Figure 3. **A**: Representative images of type A. In type A, there is little platinum accumulation in the tumor but accumulation in stroma. Scale bar: 200 µm. **B:** Representative images of type B. In type B, platinum was also present in the tumor. Scale bar: 200 µm. **C**: Kaplan-Meier analysis of the treatment-free interval in both groups in of patients treated with platinum-based agents in adjuvant chemotherapy. The type A patients developed significantly earlier recurrence, and most of them were diagnosed with platinum-resistant recurrence (p=0.020). **D:** Kaplan-Meier analysis of the two groups' overall survival (OS). The type A patients had significantly shorter survival compared to the type B patients (P= 0.031).

Research Summary and Future Perspective

We obtained the novel findings that the platinum distribution identified by LA-ICP-MS can be a reasonable biomarker of true platinum resistance in patients with advanced ovarian cancer and can provide useful information for the selection of the appropriate chemotherapy after operation. In the future, the analysis of NAC-IDS specimens using LA-ICP-MS can offer guidance toward more appropriate adjuvant anticancer treatment and can change the treatment strategy for patients with advanced ovarian cancer.



Publication

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