# 学 位 論 文 の 要 旨

氏名　野々村由紀

学 位 論 文 名　Ovarian Endometrioid and Clear Cell Carcinomas With Low Prevalence of Microsatellite Instability: A Unique Subset of Ovarian Carcinomas Could Benefit From Combination Therapy With Immune Checkpoint Inhibitors and Other Anticancer Agents

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著 者 名　Yuki Nonomura , Kentaro Nakayama , Kohei Nakamura , Sultana Razia , Hitomi Yamashita , Tomoka Ishibashi , Masako Ishikawa , Seiya Sato , Satoru Nakayama , Yoshiro Otsuki and Satoru Kyo

## 論 文 内 容 の 要 旨

### INTRODUCTION

Ovarian cancer has the highest mortality rate among all gynecological malignancies. The 5-year survival rate is 60%. Thus, a novel treatment strategy is needed urgently. Recently, due to the development of genomic medicine, molecular-targeted drugs have attracted attention. There have been reports that immune checkpoint inhibitors may be effective in microsatellite instability-high (MSI-H) tumors. In Japan, immune checkpoint inhibitors for MSI-H tumors were covered by insurance in 2018. The frequency of MSI-H in ovarian cancer is reportedly 2–20%, and it is common mainly in endometrioid and clear cell carcinomas. Ovarian endometrioid and clear cell carcinomas are called endometriosis-related ovarian neoplasms (ERONs), and endometriosis has been reported to be a cause of carcinogenesis. Microsatellite instability found in ERONs can also be confirmed in the epithelium of endometriosis. To date, while there have been some reports that utilized immunostaining of the MMR protein to determine the MSI status rather than an MSI analysis with a polymerase chain reaction (PCR), to the best of our knowledge there has been no report that evaluates the MSI status using a PCR, and focuses on ovarian endometrioid and clear cell carcinomas as a unique subset of ovarian carcinomas. In this study, ovarian endometrioid and clear cell carcinomas tissue samples were analyzed for their MSI status using a PCR, and the relationship between MSI-H, immune checkpoint molecules, and clinicopathological factors, including patient survival, was assessed.

## MATERIALS AND METHODS

This study evaluated 91 cases of ovarian carcinoma (52 clear cell carcinomas, 39 endometrioid carcinomas), which had received treatment between April 2008 and December 2018 at the Department of Obstetrics and Gynecology at the Shimane University Hospital and the Seirei Hamamatsu General Hospital. We evaluated the expression of the MMR proteins (MSH2, MLH1, MSH6, and PMS2), immune checkpoint molecules (PD-1, PD-L1,) CD8 lymphocyte infiltration in the tumor, and the ARID1A using immunohistochemistry (IHC). A diagnosis of a deficient MMR (d-MMR) tumor was made if at least one of the four MMR proteins were negative. We classified the expression of CD8 lymphocytes that infiltrated the tumor. When 5% or more of the tumor-infiltrating lymphocytes or tumors were stained, PD-1 and PD-L1 were considered to be positive. All 91 cases were outsourced to BML (BML, Tokyo, Japan), and MSI was diagnosed using PCR. Clinical data were collected from the patient charts. The follow-up period ranged from 4 to 128 months, with a median follow-up of 57 months. Statistical analyses were carried out the chi-squared test and Kaplan-Meier curve using the SPSS software and $p$-value $< 0.05$ was considered statistically significant. The study protocol was approved by the Research Ethics Committee of Shimane University.

## RESULTS AND DISCUSSION

We examined the MSI status using PCR, and also performed IHC for the MMR proteins (MSH2, MSH6, PMS2, and MLH1). From the PCR results, only 5 of 91 (5%) cases were MSI-H, and all of these were endometrioid carcinomas. The number of MSI-H tumors was significantly higher in endometrioid carcinomas than in clear cell carcinomas. Furthermore, in these five MSI-H cases, no correlations were found between the MSI-H and clinicopathological factors including age, FIGO stage, initial treatment, status of residual tumor, status of ARID1A expression, and the status of endometriosis. According to past reports, the frequency of MSI-H in ovarian carcinomas has been found to be 2–20% in clear cell carcinoma 2.4–14.3%, and in endometrioid carcinoma 13.8–33%. In our study, MSI-H in approximately 13% of endometrioid carcinomas. These results are consistent with those of previous reports. In these cases, CD-8 expression was significantly higher ($p = 0.026$), confirming an enhanced immune response. However, we did not observe significant correlations between MSI-H and PD-1 or PD-L1 expressions, suggesting that the effects of the immune checkpoint inhibitors in ovarian endometrioid carcinomas may be limited. MSI-H tumors have been shown to be more immunogenic, have better anti-tumor immune responses, and are more capable of inhibiting tumor cell growth. In colorectal and gastric cancers, the MSI-H tumors have better prognosis than MSI-low and MSS. But, in this study, from the survival curve, no statistical correlations were found between the MSI-H group and the microsatellite stable (MSS) group. This prognostic

difference between colorectal and ovarian cancers may be due to the relatively small number of analyzed cases and low prevalence of MSI-H tumors in ovarian endometrioid and clear cell carcinomas or in an organ-specific manner. On the other hand, patients with PD-L1 expression had shorter overall survival than those without ($p = 0.022$). Since immune checkpoint inhibitors are expected to be effective in tumors with a high PD-L1 expression, the positive PD-L1 cases with poor survival found in the current study may be aided using immune checkpoint inhibitors. Now, some clinical studies have reported the efficacy and safety of combination therapy with immune checkpoint inhibitors (eg, KEYNOTE100 and LEAP-005). These suggest that combination therapy was greater than that of either single treatment. A combination therapy of pembrolizumab and lenvatinib improved the prognosis of patients with endometrial cancers, and covered by insurance. Although the study involved a different type of carcinoma, it demonstrated an improvement in the prognosis of patients who received concomitant immune checkpoint inhibitor treatment. Thus, there is a possibility that this treatment can improve the prognosis of patients with endometriosis-related ovarian cancer. Due to the low prevalence of MSI-H in ovarian endometrioid and clear cell carcinomas, the use of immune checkpoint inhibitors alone did not show a good response, while the use of combination therapy such as lenvatinib and immune checkpoint inhibitors may have had some effect.

## CONCLUSION

Thus, MSI-H is a rare event and not a favorable prognostic factor in ovarian endometrioid and clear cell carcinomas. Thus, to improve the prognosis of ovarian endometrioid carcinoma and clear cell carcinomas, a combination therapy of immune checkpoint inhibitors and other molecular targeted therapies may be required.