

# Surgical efficacy and quality of wide resection of the pelvic peritoneum in patients with epithelial ovarian cancer

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## Research Article

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# Abstract

## Purpose

The aim of study was to evaluate the impact of adding an extensive pelvic peritoneal stripping procedure, termed “wide resection of the pelvic peritoneum,” (WRPP) to standard surgery for epithelial ovarian cancer on survival effectiveness and to investigate the role of ovarian cancer stem cells (CSCs) in the pelvic peritoneum.

## Methods

A total of 166 patients with ovarian cancer undergoing surgical treatment at Kumamoto University Hospital between 2002 and 2018 were retrospectively analyzed. Eligible patients were divided into three groups based on the surgical approach: standard surgery (SS) group (n = 36), WRPP group (standard surgery plus WRPP, n = 100), and rectosigmoidectomy (RS) group (standard surgery plus RS, n = 30). Survival outcomes were compared between the three groups. CD44 variant 6 (CD44v6) and EpCAM expression, as markers of ovarian CSCs, in peritoneal disseminated tumors were evaluated using immunofluorescence staining.

## Results

With respect to patients with stage III–IV ovarian cancer, there were significant differences in overall and progression-free survival between the WRPP and SS groups, as revealed by univariate (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.17–0.69; P = 0.003 and HR, 0.54; 95% CI, 0.31–0.95; P = 0.032, respectively) and multivariate Cox proportional hazards model (HR, 0.35; 95% CI, 0.17–0.70; P = 0.003 and HR, 0.54; 95% CI, 0.31–0.95; P = 0.032, respectively). Further, no significant differences were observed in survival outcomes between the RS group and the SS or WRPP group. Regarding the safety of WRPP, no significant differences in major intraoperative and postoperative complications were found between the three groups. Immunofluorescence analysis revealed a high percentage of CD44v6/EpCAM double-positive ovarian cancer cells in peritoneal disseminated tumors.

## Conclusion

The present study demonstrates that WRPP significantly contributes to improved survival in patients with stage III–IV advanced ovarian cancer. WRPP could result in eradicating ovarian CSCs and disrupting the CSC niche microenvironment in the pelvic peritoneum.

## Introduction

Ovarian cancer is the leading cause of gynecologic cancer-related death [1, 2]. The clinical outcome of patients with ovarian cancer is poor because the majority of patients are diagnosed in advanced stages with multiple intraperitoneal disseminated tumors [3, 4]. Over the past few decades, the treatment paradigm of maximal cytoreductive surgical effort prior to administration of taxane- or platinum-based chemotherapy has become firmly established [5, 6]. More recently, the prognostic significance of complete cytoreductive surgery, defined as no visible residual disease, over optimal cytoreductive surgery, which leaves residual tumors less than 1 cm in size, has been appreciated as a noble goal [7, 8].

Ovarian cancer can spread through lymphatics to nodes in the pelvic and para-aortic regions and through blood vessels to the parenchyma of viscera such as the liver, lung, and brain [9, 10]. Especially, small clusters of ovarian cancer cells shed from primary tumors frequently metastasize to the peritoneal surface and form numerous disseminated nodules in the peritoneal cavity [1, 11, 12]. Previous studies have shown that the pelvic peritoneum is the most common site of disseminated metastasis and recurrence in patients with ovarian cancer [13, 14]. These findings suggest that stripping of the pelvic peritoneum contributes to effective cytoreductive surgery for patients with advanced ovarian cancer with microscopic disease as well as macroscopic disseminated tumors, which contiguously extend into the vesicouterine and rectouterine peritonea in the pelvic cavity.

In patients with superficial dissemination of ovarian cancer cells on the peritoneal lining of the pelvic cavity, tumor burden can be reduced by stripping the peritoneum [15, 16]. However, tumor invasion into the bowel wall limits the debulking of disseminated tumors using the peritoneal stripping technique [16, 17], necessitating *en bloc* resection of the rectosigmoid [18, 19]. Therefore, surgical procedures should be selected based on the degree of tumor invasion into the bowel wall or on the feasibility of complete cytoreductive surgery.

Accumulating evidence indicates that the bulk of cancer cells are generated by rare populations of self-renewing, multipotent tumor-initiating cells, conceptually termed “cancer stem cells” (CSCs) [20, 21]. CSCs are inherently responsible for metastasis and therapy resistance [1, 22, 23]. Even though ovarian CSCs have not been fully characterized, they seem to play a functional role in colonization at metastatic sites in the intraperitoneal cavity and in hematogenous distant metastasis [1, 24, 25]. In fact, our previous studies demonstrated that mouse ovarian tumor-initiating cells generated by transduction of defined genetic alterations have a high potential for peritoneal metastasis [26]. Furthermore, our research group discovered the functional roles of CD44 variant 6 (CD44v6) and EpCAM in the regulation of ovarian cancer stemness, metastatic progression, and therapy resistance [23, 24, 27]. Normal stem cells reside in a microenvironment called “stem cell niche”, which maintains their stemness [28]. Recent evidence suggests that CSCs also rely on a similar niche known as “CSC niche” [29, 30], which is associated with the regulation of CSC properties [1, 20]. In particular, peritoneal mesothelial cells in the pelvic peritoneum may have the potential to create the niche microenvironment for ovarian CSCs [31].

The aim of this study was to evaluate the effectiveness and safety of a pelvic peritoneum stripping procedure termed “wide resection of the pelvic peritoneum” (WRPP) for the elimination of disseminated

tumors in the pelvic peritoneum and to determine the survival benefit of WRPP for patients with ovarian cancer. Further, in association with the efficacy of WRPP, we investigated the potential relationship between ovarian CSCs and the pelvic peritoneum as a putative CSC niche.

## Materials And Methods

### Patient selection and surgical procedures

Between January 2002 and December 2018, 461 patients with ovarian cancer underwent surgical treatment at Kumamoto University Hospital. The clinical and surgical records of these patients were reviewed retrospectively, and 166 patients with stage IC–IVB ovarian cancer who underwent cytoreductive surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymphadenectomy with or without para-aortic lymphadenectomy, were included in this study. Patients were excluded from this study if they underwent fertility-sparing surgery or if they had non-epithelial tumors, borderline tumors, or multiple primary cancers. Patients referred to our institution after primary operation were also excluded from this study.

Eligible patients were divided into three groups based on the surgical approach. Patients who underwent surgical cytoreduction with standard definitive surgery were categorized as the standard surgery (SS) group. Patients who underwent standard surgery plus WRPP as part of cytoreduction were categorized as the WRPP group. Patients who required standard surgery plus rectosigmoidectomy (RS) to debulk tumor burden were categorized as the RS group (Fig. 1). The eligible patients were followed up until death or to the end of follow-up in December 2021.

With respect to the WRPP procedure, to remove microscopic disease as well as macroscopic disseminated tumors in the pelvic peritoneum, we resected the vesicouterine peritoneum toward the top of the bladder and the rectouterine peritoneum toward the rectosigmoid junction depending on the spread of disease as shown in **Fig. 2A** and **Fig. 2B**. A representative macroscopic appearance of an *en bloc* specimen obtained by WRPP is shown in **Fig. 2C**. RS was performed in cases of tumor invasion through the muscular wall of the intestine observed during preoperative and intraoperative evaluation. The surgical technique of RS is described in detail in previous studies [18, 32].

This study was approved by the Institutional Review Board of Kumamoto University Hospital, and written informed consent was obtained from all the patients before treatment in compliance with the institutional guidelines of our hospital.

### Histology and Immunofluorescence staining

Surgically obtained tumor tissues were fixed in 10% paraformaldehyde and embedded in paraffin. Tissue blocks were sliced into 4- $\mu$ m-thick sections for histological examinations. Sections were stained with hematoxylin and eosin, and histological diagnosis was made according to the 2020 World Health

Organization classification of tumors of the ovary [33]. All the tumors were staged based on the 2014 International Federation of Gynecology and Obstetrics (FIGO) criteria [34].

Immunofluorescence staining was performed as described in a previous study [26]. Tissue sections were stained with anti-CD44v6 monoclonal antibody (2F10; R&D Systems, Minneapolis, MN, USA) and anti-EpCAM monoclonal antibody (B302 [323/a3]; Abcam, UK). Nuclei were counterstained with 4', 6-diamidino-2-phenylindole. Sections and cells were viewed using a Bioevo BZ-9000 fluorescence microscope (Keyence, Tokyo, Japan).

## Statistical analysis

To evaluate associations between the three operative methods and clinicopathological characteristics, operative findings, or distribution of recurrence patterns, Kruskal–Wallis test and Fisher exact test were used as appropriate.

Further, to perform survival analysis, overall survival (OS) was set as the primary outcome measure, and progression-free survival (PFS) was set as the secondary endpoint. In the survival analysis, Kaplan–Meier curves were plotted, and differences in the risk of outcomes in the three surgical methods were evaluated using univariate and multivariate Cox proportional hazards models. The models were adjusted for age of participants, histological type (high-grade serous carcinoma or not), and FIGO stage (I, II, III, or IV). In the analyses, assumptions of proportional hazards were tested using weighted residuals in each model [35]. The statistical analyses were performed using STATA 15.0 (STATA Corp., Lakeway Drive, Texas). Differences were considered statistically significant when two-sided P value < 0.05.

## Results

### Clinicopathological features of all eligible patients

The clinical and pathological characteristics of all eligible patients are shown in Table 1. The median age of all patients at the time of diagnosis was 57 years (range: 32–79 years). There were significant differences in median age between the three groups (52.5 years in the SS group, 56.5 years in the WRPP group, and 63.5 years in the RS group). Tumor stage distribution was stage I in 29 patients (17.5%), stage II in 27 patients (16.2%), stage III in 82 patients (49.3%), and stage IV in 28 patients (16.9%); no significant differences in FIGO stage distribution were observed between the three groups. Regarding histological tumor type, 100 patients (60.2%) had high-grade serous carcinoma, two patients (1.2%) had low-grade serous carcinoma, 22 patients (13.3%) had endometrioid carcinoma, 29 patients (17.5%) had clear cell carcinoma, and five patients (3.0%) had mucinous carcinoma. There were significant differences in the rate of histological type between the three groups; the rate of high-grade serous carcinoma in the RS group (80.0%) was higher than that in the SS group (58.3%) and the WRPP group (55.0%).

### Operative findings and postsurgical complications

With regard to operative findings, the median operative time was 313.5 minutes (range: 180–575 minutes) in the SS group, 298.5 minutes (range: 178–772 minutes) in the WRPP group, and 485 minutes (range: 300–1219 minutes) in the RS group. No significant differences in median operative time were observed between the SS and WRPP groups ( $P = 0.939$ ), but median operative time was significantly longer in the RS group than in the SS or WRPP group ( $P < 0.001$ ). There were no significant differences in median blood loss volume and blood transfusion rate between the SS and WRPP groups ( $P = 0.071$  and  $P = 0.547$ , respectively). However, median blood loss volume and blood transfusion rate were significantly higher in the RS group than in the SS or WRPP group ( $P < 0.001$  and  $P < 0.001$ , respectively). No significant differences in residual tumor size were observed between the three groups. In addition, no severe intraoperative complications were observed, and the risk of major postsurgical complications in each group was low; two out of the 30 patients (6.7%) in the RS group had severe postoperative diarrhea. There was no surgical procedure-related death in any group (Table 2).

## Surgical effectiveness of WRPP

To examine the survival impact associated with different surgical procedures, we performed Kaplan–Meier analysis of OS and PFS between the three groups. The five-year OS and PFS rates of all eligible patients with stage IC–IVB ovarian cancer were 52.8% and 41.7% in the SS group, 81.0% and 59.0% in the WRPP group, and 63.3% and 36.7% in the RS group, respectively. In the univariate Cox proportional hazards model, OS and PFS were significantly longer in the WRPP group than in the SS group (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.17–0.64;  $P = 0.001$  and HR, 0.58; 95% CI, 0.34–0.98;  $P = 0.043$ , respectively). Further, there were no significant differences in OS between the WRPP and RS groups (HR, 0.48; 95% CI, 0.23–1.02;  $P = 0.055$ ), whereas PFS was significantly longer in the WRPP group than in the RS group (HR, 0.53; 95% CI, 0.31–0.91;  $P = 0.021$ ). No significant differences in OS and PFS were observed between the SS and RS groups (HR, 0.69; 95% CI, 0.32–1.48;  $P = 0.341$  and HR, 1.10; 95% CI, 0.59–2.05;  $P = 0.758$ , respectively) (Fig. 3A and Fig. 3B).

Given that most patients (86.7%) in the RS group were diagnosed with stage IIIA–IVB disease, we divided eligible patients into two subgroups, stage IC–IIB subgroup and stage IIIA–IVB subgroup. No significant differences in the OS and PFS of patients with stage IC–IIB ovarian cancer were observed between the three groups (Fig. 3C and Fig. 3D). Regarding patients with stage IIIA–IVB ovarian cancer, the five-year OS and PFS rates were 38.5% and 23.1% in the SS group, 72.4% and 44.8% in the WRPP group, and 61.5% and 30.8% in the RS group, respectively. In the univariate Cox proportional hazards model, OS and PFS were statistically significantly longer in the WRPP group than in the SS group (HR, 0.35; 95% CI, 0.17–0.69;  $P = 0.003$  and HR, 0.54; 95% CI, 0.31–0.95;  $P = 0.032$ , respectively). There were no significant differences in OS and PFS between the WRPP and RS groups (HR, 0.67; 95% CI, 0.30–1.48;  $P = 0.324$  and HR, 0.65; 95% CI, 0.36–1.15;  $P = 0.140$ , respectively) and between the SS and RS groups (HR, 0.51; 95% CI, 0.23–1.13;  $P = 0.100$  and HR, 0.84; 95% CI, 0.44–1.58;  $P = 0.583$ , respectively) (Fig. 3E and Fig. 3F).

We subsequently created a multivariate Cox proportional hazards model for OS and PFS to avoid confounding bias. Regarding patients with stage IIIA–IVB ovarian cancer, OS and PFS were significantly longer in the WRPP group than in the SS group (HR, 0.35; 95% CI, 0.17–0.70;  $P = 0.003$  and HR, 0.54; 95%

CI, 0.31–0.95;  $P = 0.032$ , respectively) (Table 3), indicating that WRPP contributes substantially to favorable prognosis in patients with stage III–IV advanced ovarian cancer.

## **Distribution of recurrence patterns and sites**

The recurrence patterns and sites are summarized in Table 4. Tumor recurrence was observed in 21 of 36 patients (58.3%) in the SS group, in 41 of 100 patients (41.0%) in the WRPP group, and in 18 of 30 patients (60%) in the RS group. Peritoneal dissemination was found to be the most frequent pattern of recurrence. It occurred in 16 of 36 patients (44.4%) in the SS group, in 30 of 100 patients (30.0%) in the WRPP group, and in 12 of 30 patients (40.0%) in the RS group. No significant differences were observed in peritoneal disseminated recurrence between the three groups; however, WRPP was associated with a numerical improvement in intrapelvic peritoneal recurrence. The total number of hematogenous recurrences was relatively small; there were no significant differences in hematogenous recurrence between the three groups. Similarly, there were no significant differences in the lymphatic recurrence rate between the three groups.

## **Immunofluorescence findings of ovarian CSCs in microscopic peritoneal carcinomatosis**

We investigated the factor underlying the surgical effectiveness of WRPP in terms of ovarian CSCs, which have the ability of metastatic colonization of the pelvic peritoneum. In the normal-appearing pelvic peritoneum, ovarian cancer cells, which are not visible to the naked eye, were occasionally identified during postoperative histopathological examination of peritoneal tissues, and we defined this type of peritoneal disseminated disease as “microscopic peritoneal carcinomatosis”. In this study, microscopic peritoneal carcinomatosis was identified specifically in pelvic peritoneal tissues obtained by WRPP (Fig. 4A). Given that our previous study revealed that a subpopulation of CD44v6- and EpCAM-positive ovarian cancer cells possess CSC traits [23, 27], we performed immunofluorescence staining to analyze the CD44v6 and EpCAM expression of ovarian cancer cells in the pelvic peritoneum isolated from patients in the WRPP group. It is noteworthy that areas of microscopic peritoneal carcinomatosis were found to be rich in CD44v6/EpCAM double-positive ovarian cancer cells (Fig. 4B). These findings suggest that microscopic peritoneal carcinomatosis contains highly enriched CD44v6/EpCAM double-positive ovarian CSCs and that the pelvic peritoneum has the potential to form part of the CSC niche, thereby promoting metastatic colonization. Thus, the removal of peritoneal tissues containing microscopic CD44v6/EpCAM double-positive ovarian cancer cells by WRPP contributes to the eradication of ovarian CSCs in the pelvic peritoneum.

## **Discussion**

In 1968, the British surgeon Christopher Hudson devised a seminal surgical technique in which the entire vesicouterine peritoneum and Douglas pouch are removed as a false tumor capsule in patients with advanced ovarian cancer [15]. Since then, the rationale of extensive pelvic peritonectomy has been clinically accepted worldwide and validated by a number of gynecologic surgeons and oncologic centers

[16, 17, 19, 36, 37]. However, the survival outcomes and surgical efficacy of extensive peritoneal stripping procedures in the pelvic cavity have heretofore not been fully understood. Thus, the aim of this study was to evaluate the impact of adding WRPP to standard surgery on the survival of patients with ovarian cancer.

In this study, we showed that the addition of extensive surgical cytoreduction by WRPP is closely associated with improved survival in our single-institution series of patients with advanced ovarian cancer. Kaplan–Meier analysis revealed that OS and PFS were significantly longer in the WRPP group than in the SS group for all eligible patients (with stage IC–IVB ovarian cancer) and for patients with stage IIIA–IVB ovarian cancer. By contrast, there were no significant differences in the survival outcomes of patients with stage IC–IIB ovarian cancer. Notably, the multivariate Cox proportional hazards model revealed that WRPP contributes to improvement of OS and PFS in patients with stage IIIA–IVB ovarian cancer, indicating that WRPP is effective for advanced disease with multiple disseminated tumors in the pelvic cavity.

Regarding intraoperative and postoperative findings, the RS group had the longest median operative time, highest median blood loss volume, and highest blood transfusion rate of the three groups, indicating that RS is a more invasive surgical procedure than WRPP and SS for debulking disseminated ovarian tumors in the pelvic cavity. It is important to note that no significant differences in median operative time, median blood loss volume, or blood transfusion rate were found between the SS and WRPP groups. Furthermore, no severe intraoperative or postoperative complication was attributed to WRPP, indicating that WRPP is a safe and less invasive surgical procedure for ovarian cancer patients.

Effective ovarian cancer therapy requires the eradication of CSCs [1, 20], which are thought to drive tumor initiation, metastasis, and therapy resistance [1, 21, 26]. Our previous study revealed that the cell surface proteins CD44v6 and EpCAM play crucial roles in regulating ovarian cancer stemness, promoting metastasis, and enhancing chemotherapy resistance [20, 23, 24, 27]. In this study, we identified highly enriched CD44v6/EpCAM double-positive ovarian cancer cells in microscopic peritoneal carcinomatosis, suggesting that these cells have a high potential for peritoneal dissemination, and the pelvic peritoneum plays an important role in the maintenance of cancer stemness as a part of the niche microenvironment. Theoretically, WRPP could be useful for the eradication of microscopic ovarian CSC populations and for the excision of CSC niche microenvironment of the pelvic peritoneum, contributing more effective surgical strategy for patients with advanced ovarian cancer.

Emerging evidence revealed the “premetastatic niche,” which is a specialized microenvironment that forms at sites of future metastases and promotes re-initiation, colonization, and outgrowth of disseminated cancer cells [12, 29]. In this study, the most frequent pattern of recurrence was peritoneal disseminated metastasis, and the rate of peritoneal recurrence was lower in the WRPP group than in the SS or RS group. These findings suggest that the microenvironment of the pelvic peritoneum functions as the premetastatic niche for disseminated ovarian cancer metastasis, leading to effective metastatic colonization in the pelvic peritoneum [13, 29, 31]. Thus, WRPP should help disrupt the premetastatic



niche microenvironment, thereby reducing the possibility of peritoneal disseminated recurrence in patients with advanced ovarian cancer [1, 13, 31].

This study has several limitations and strengths. The main limitation of this study is its retrospective design. Another limitation is the potential selection bias in this study given that different surgical procedures were selected depending on the extent of tumor spread and depth of invasion into the intestine. One strength of this study is the limited number of studies on the survival impact of pelvic peritonectomy. Another strength of this study is that all standardized surgical procedures were performed by one surgical team over the years, contributing to considerably low surgical complications.

In conclusion, WRPP is a safe and effective surgical procedure that should be part of the skill set of gynecologic surgeons who perform extensive surgical cytoreduction in patients with advanced ovarian cancer. In the future, evolving concepts and novel therapeutic strategies targeting ovarian CSCs in peritoneal disseminated tumors and putative niche microenvironment are needed to eradicate this life-threatening malignancy.

## **Declarations**

### **Conflict of Interest statement**

The authors declare no conflict of interest with respect to the authorship and publication of this article.

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### **Author Contributions**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Takeshi Motohara, Akiho Nishimura, Jun Morinaga, Yutaka Iwagoi, Mayuko Yamamoto, Munekage Yamaguchi, Yo Miyahara, Hironori Tashiro and Hidetaka Katabuchi. The first draft of the manuscript was written by Takeshi Motohara and Akiho Nishimura and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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### **Ethical statement**

This study was approved by the Institutional Review Board of Kumamoto University Hospital,

### **Conflict of interest**

Written informed consent was obtained from all the patients before treatment in compliance with the institutional guidelines of our hospital.

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## Tables

Tables 1 to 4 are available in the Supplementary Files section.

## Figures

Figure 1

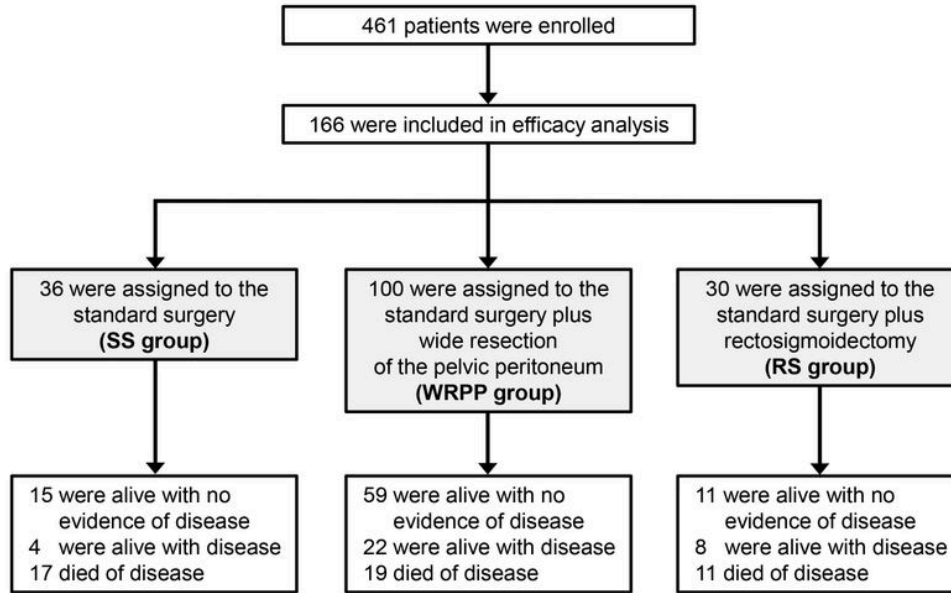


Figure 1

Flowchart of the study design and inclusion of patients.

Figure 2

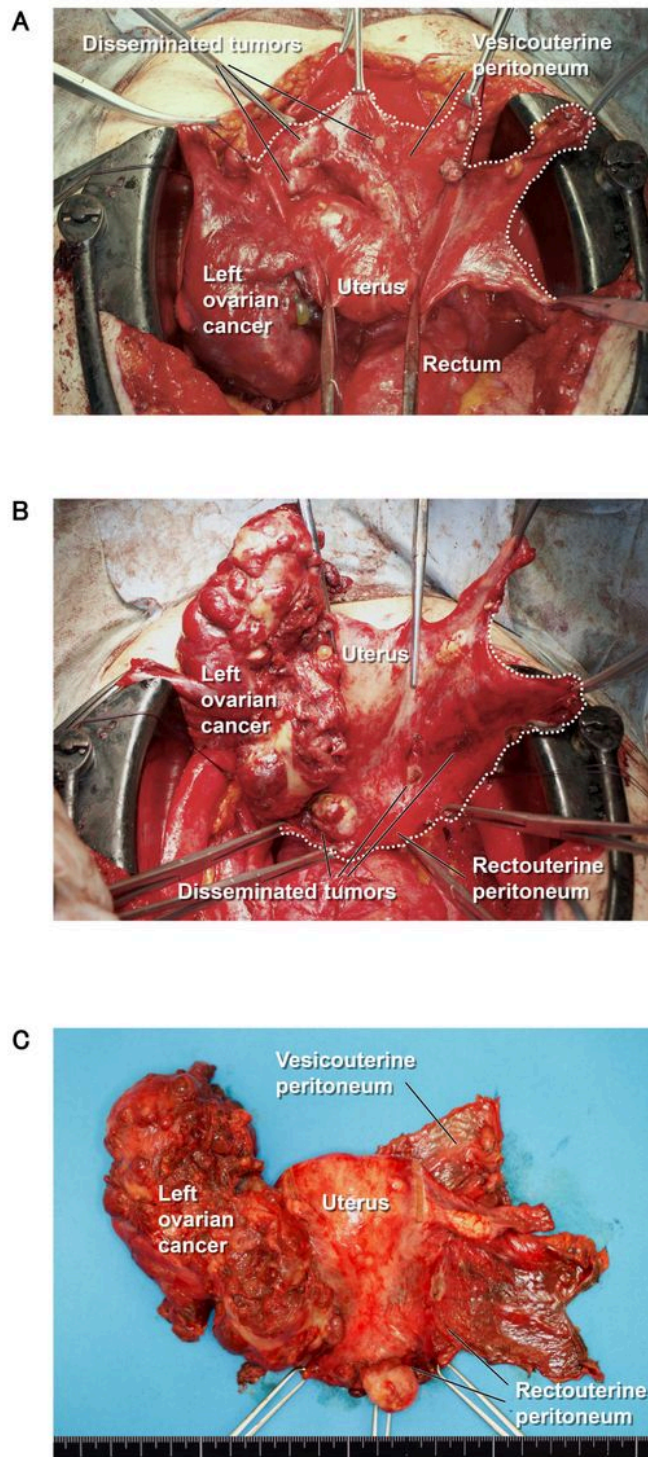


Figure 2

Surgical procedure of WRPP.

(A, B) A representative picture of the pelvic cavity during the WRPP procedure are shown. The extent of an *en bloc* resection of the vesicouterine (A) and rectouterine peritoneum (B) with free margins are decided based on the spread of disseminated tumors in the pelvic cavity.

(C) A representative macroscopic appearance of an *en bloc* specimen obtained by WRPP.

Figure 3

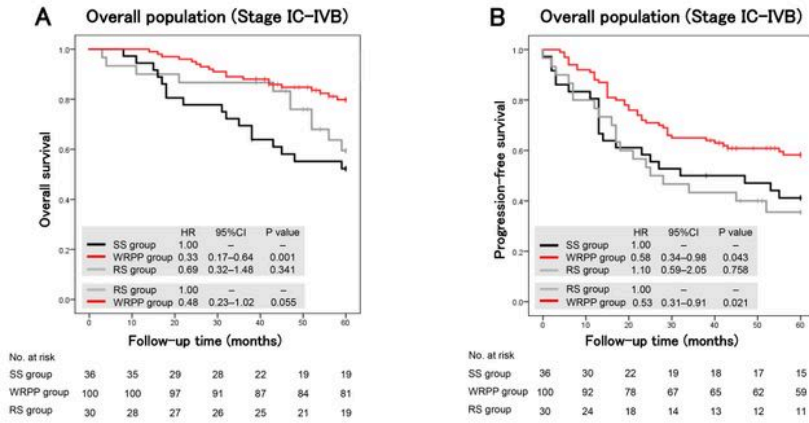


Figure 3

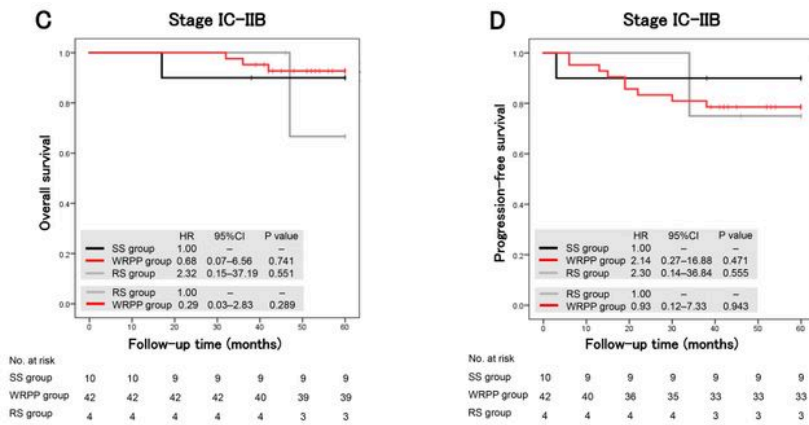


Figure 3

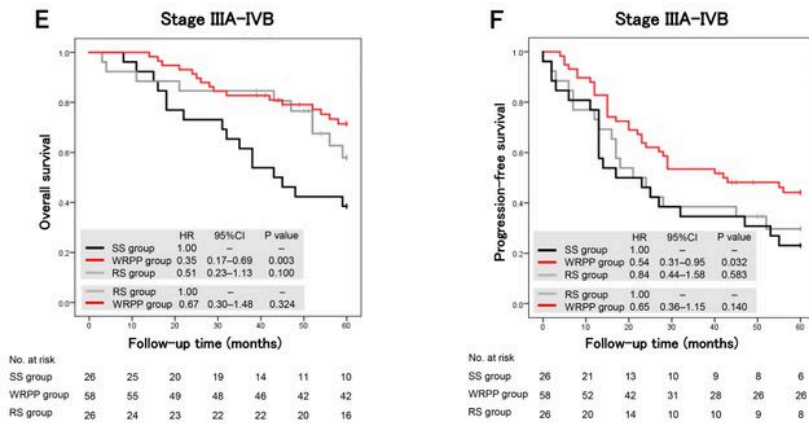


Figure 3

Prognostic significance of WRPP.

(A, B) Kaplan–Meier analysis of OS (A) and PFS (B) for all eligible patients with ovarian cancer based on the type of surgical procedure. OS and PFS are statistically significantly longer in the WRPP group than in

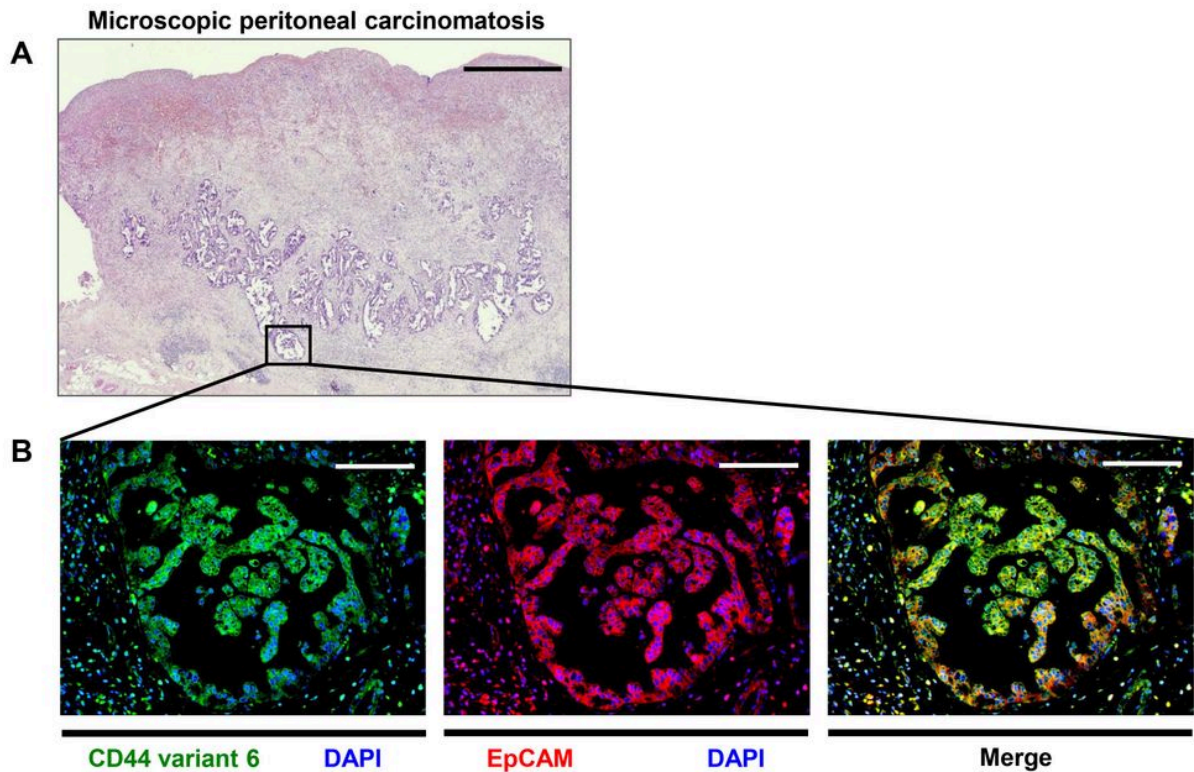


the SS group ( $P = 0.001$  and  $P = 0.043$ , respectively).

(C, D) Kaplan–Meier analysis of OS (C) and PFS (D) for patients with stage IC–IIB ovarian cancer based on the type of surgical procedure. There are no significant differences in the OS and PFS between the three groups.

(E, F) Kaplan–Meier analysis of OS (E) and PFS (F) for patients with stage IIIA–IVB ovarian cancer based on the type of surgical procedure. Significant differences in the OS and PFS are observed between the WRPP and SS groups ( $P = 0.003$  and  $P = 0.032$ , respectively).

**Figure 4**



**Figure 4**

A representative image of the specimen of normal-appearing pelvic peritoneum removed by WRPP.

(A) Microscopic peritoneal carcinomatosis was found in the pelvic peritoneum (scale bar: 500  $\mu\text{m}$ ).

(B). Tissue sections of microscopic peritoneal carcinomatosis were subjected to immunofluorescence analysis with antibodies to anti-CD44v6 (green) and anti-EpCAM (red). Nuclei are stained with 4', 6-diamidino-2-phenylindole (blue). Highly enriched CD44v6/EpCAM double-positive ovarian cancer cells are identified in microscopic peritoneal carcinomatosis in the pelvic peritoneum (scale bars: 100  $\mu\text{m}$ ).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.



- [WRPPFINALTable.pdf](#)