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# Surgical management of recurrent gynecological cancer: Complete resection is the key to longer survival

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**Summary**

*Purpose of investigation:* This study was conducted to elucidate the efficacy and feasibility of surgical management of recurrent gynecological (cervical, endometrial, and ovarian) cancers. *Materials and Methods:* Patients undergoing surgical management for recurrent gynecological cancers at Fukushima Medical University between January 2001 and December 2012 were evaluated. Progression-free survival (PFS) and overall survival (OS) were each estimated using the Kaplan–Meier method and compared with the log-rank test. *Results:* Fifty patients underwent surgery for recurrent gynecological cancers (13 cervical, 18 endometrial, and 19 ovarian). On univariate analysis, complete surgery was a significant prognostic factor in all cancer types. On multivariate analysis, there were significant differences in complete surgery and the number of recurrent tumors for endometrial cancer. *Conclusion:* These results suggest that, in a select group of patients, especially in recurrent endometrial cancer, surgical management improves survival of recurrent gynecologic cancer patients, and it is valuable therapeutic option.

*Key words:* Recurrent gynecological cancer; Surgical management; Complete surgery.

## Introduction

Uterine cervical, endometrial, and ovarian cancers are common cancers treated by gynecological oncologists, and their initial treatment has been established recently, with many treatment guidelines available [1-10]. However, for recurrent cancers, many treatment strategies are used in each institution. Most therapies cannot achieve complete cure, because recurrent tumors usually show resistance to any therapy, and even if the treatment is initially effective, most cases recur. Surgical treatment is the cornerstone of initial treatment, but it is controversial for recurrent tumors. As for gynecological cancers, some studies have shown the benefit of surgery for recurrent tumors, but it remains controversial [11-18]. The treatment options for recurrent tumor are established and depend on the characteristics of the tumor, and some criteria for surgical management of recurrent tumors evaluate resectability using parameters that have been reported [14-18]. In the present department, the indications for surgical treatment of recurrent tumor have been determined primarily by evaluation of tumor resectability based on radiologic examinations such as CT or positron emission CT (PET-CT), taking into account patients' performance status (PS). In the present retrospective study, the effectiveness of surgical treatment for recurrent gynecological cancer in the present department was evaluated.

## Materials and Methods

An analysis of patients who underwent surgery for recurrent gynecological cancers, including cervical, endometrial, and ovarian cancers, at Fukushima Medical University between January 2001 and December 2012 was performed. The decision to pursue salvage surgical treatment for recurrent gynecological cancer was determined by the Fukushima Medical University Gynecology Tumor Board. The study was approved by the Institutional Review Board of Fukushima Medical University. All patients with recurrent epithelial gynecologic cancers, including cervical, endometrial, and ovarian cancers, except germ cell tumors, choriocarcinomas, and sarcomas, were analyzed. Demographic and clinicopathological characteristics were evaluated using basic descriptive statistics. In this study, a tumor that measured more than 1 cm on CT images with or without PET-CT obtained over time was defined as a recurrent tumor. Data regarding pathological, clinical, and surgical characteristics were retrieved from the database of the Department of Gynecologic Oncology. Missing data were integrated from surgical reports and clinical charts that were reviewed independently. Recurrence was defined as that which occurred more than one month after achievement of complete re-

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Table 1. — *Patients' characteristics*.

| | Cervical cancer (n=13) | Endometrial cancer (n=18) | Ovarian cancer (n=19) | |
|---|---|---|---|---|
| Age | 49.1±15.3 | 69.9±10.7 | 59.2±12.7 | 0.004 |
| Stage | | | | |
| Ⅰ Ⅱ | 12 | 10 | 4 | 0.000 |
| Ⅲ Ⅳ | 1 | 9 | 15 | |
| | | | | |
| Histology | Squamous 11 | Endometrioid 12 | Serous 14 | |
| | Adenosquamous 2 | Adenosquamous 1 | Endometrioid 2 | |
| | | Serous 2 | Clear 1 | |
| | | Clear 1 | Carcinosarcoma 1 | |
| | | Carcinosarcoma 2 | Undifferentiated 1 | |
| | | | | |
| Number of tumors | | | | |
| Single | 6 | 16 | 11 | 0.03 |
| Multiple | 7 | 2 | 8 | |
| | | | | |
| Site of recurrence | | | | |
| Intra pelvis | 5 | 9 | 5 | 0.332 |
| Extra pelvis | 8 | 9 | 14 | |
| | | | | |
| | | | | |
| History of irradiation | 10 | 1 | 0 | 0.000 |

mission. Patients were defined as completely resected if no macroscopic residual disease was present after surgery. Postoperative complications were considered those occurring within 30 days from surgery. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of salvage surgery to clinical diagnosis of progression and death, respectively. Follow-up was performed at Fukushima Medical University. PFS and OS were each estimated using the Kaplan-Meier method and compared with the log-rank test. All cancer types were defined as recurrence of gynecological cancer, and the factors influencing PFS and OS were evaluated based on fitting univariate Cox proportional hazards models using the data of all cancer types. Factors predicting complete resectability were evaluated based on a linear regression model using the data of all cancer types.

## Results

The characteristics of the patients and each tumor are presented in Table 1. A total of 50 patients underwent surgery for pathologically documented or clinically suspected recurrent gynecological cancer (13 patients with cervical, 18 with endometrial, and 19 with ovarian cancers). In the vast majority of patients, the diagnosis of recurrence was made on radiologic examination (CT or PET-CT) ordered during routine cancer surveillance. The median age at the time of surgery for recurrence was 49, 69, and 59 years for cervical, endometrial, and ovarian cancer patients, respectively. The most frequent histotypes were squamous cell carcinoma in cervical cancer, endometrioid adenocarcinoma in endometrial cancer, and serous adenocarcinoma in ovarian cancer. The median follow-up period was 15 (range 1-132), 60 (range 1-118), and 44.5 (range 15-120) months in cervical, endometrial, and ovarian cancers, respectively. Isolated recurrence was seen in 6/13 (46.2%), 16/18 (88.9%), and 11/19 (57.9%) cervical, endometrial, and ovarian cancers, respectively. Intrapelvic recurrence was seen in 5/13 (38.5%), 9/18 (50%), and 5/19 (26.3%) cervical, endometrial, and ovarian cancers, respectively. In this study, many cases initially underwent chemotherapy or radiotherapy after recurrence, therefore 6/13 (48.8%) cervical, 11/18 (61.1%) endometrial, and 9/19 (47.4%) ovarian cancers were first recurrences. Ten of the cervical cancer cases underwent radiation therapy previously, while just one case of endometrial cancer underwent radiotherapy, and no case of ovarian cancer underwent radiotherapy. Repeated surgical treatment was performed in 2/13 (8.7%) cervical, 5/18

Table 2. — *Details of surgical procedures and results*

| Surgical procedures and outcomes | | | | |
|---|---|---|---|---|
| Variable | Cervical cancer | Endometrial cancer | Ovarian cancer | P value |
| | Number of patients (%) | | | |
| Procedure | | | | |
| Pelvic tumor resection | 6 | 10 | 4 | |
| Extrapelvic tumor resection | 2 | 3 | 14 | |
| Pelvic lymphadenectomy | 0 | 0 | 2 | |
| Paraaortic lymphadenectomy | 1 | 2 | 1 | |
| Bowel resection | 7 | 4 | 2 | |
| Ureterectomy | 1 | 0 | 0 | |
| Exenteration | 2 | 0 | 0 | |
| Pulmonary resection | 2 | 2 | 1 | |
| Others | 1 | 1 | 0 | |
| | | | | |
| Adverse event | 6(53.8%) | 2(11.1%) | 4( 21.1%) | 0.073 |
| Bowel injury | 4 | 1 | 0 | |
| Bowel perforation | 1 | 0 | 0 | |
| Urethral injury | 1 | 0 | 2 | |
| Venous injury | 1 | 0 | 0 | |
| Ileus | 1 | 1 | 1 | |
| Infection | 0 | 0 | 1 | |
| | | | | |
| Blood loss exceeding 1000 ml | 6(46.2%) | 2(11.1%) | 2(10.5%) | 0.023 |
| | | | | |
| Residual disease | | | | |
| None | 7(53.8%) | 17( 94.4%) | 15(78.9%) | 0.215 |

(22.2%) endometrial, and 4/19 (21.1%) ovarian cancers. In ovarian cancer, 10/19 (52.6%) patients were platinum-resistant, and two of them achieved long-term survival.

The surgical data, outcomes, and complications are summarized in Table 2. The most common surgical procedures were pelvic tumor resection, pelvic or para-aortic lymph node resection, and bowel resection. Two cervical cancer cases underwent pelvic exenteration. There was no surgical mortality. Complete surgery was performed in 7/13 (53.8%) cervical, 17/18 (94.4%) endometrial, and 15/19 (78.9%) ovarian cancers, and the positive predictive value (PPV) of the evaluation for resectability of recurrent tumor by radiologic examinations was determined. Intraoperative complications included bowel injuries in four cases of cervical cancer, one case of endometrial cancer, one venous injury, and one urethral injury in cervical cancer. Postoperative complications included ileus in one case of each cancer type. One ovarian cancer patient developed a postoperative infection. Blood loss exceeding 1000 mL occurred in 7/13 (53.8%) cervical, 4/18 (22.2%) endometrial, and 4/19 (21.1%) ovarian cancers.

The five-year PFS rate was 31%, 42%, and 26%, and the five-year OS rate was 31%, 65%, and 29% in patients with cervical, endometrial, and ovarian cancers, respectively (Figures 1A, B). On univariate analysis, the number of recurrent tumors, complications, and complete surgery were associated with improved PFS and OS in cervical cancer. Median PFS and five-year PFS after initial surgery for recurrent tumor were 120 months and 57%, respectively, and median OS and five-year OS were 120 months and 57%, respectively, in patients who underwent complete surgery for cervical cancers (Figures 2A, B). On the other hand, median PFS and five-year PFS after initial surgery for recurrent tumor were one month and 0%, respectively, and median OS and five-year OS were 15 months and 0%, respectively, in patients who could not undergo complete surgery for cervical cancer (Figures 2A, B). In endometrial cancer, the number of recurrent tumors and complete surgery were associated with improved PFS and OS. In the complete surgery group with endometrial cancer, median

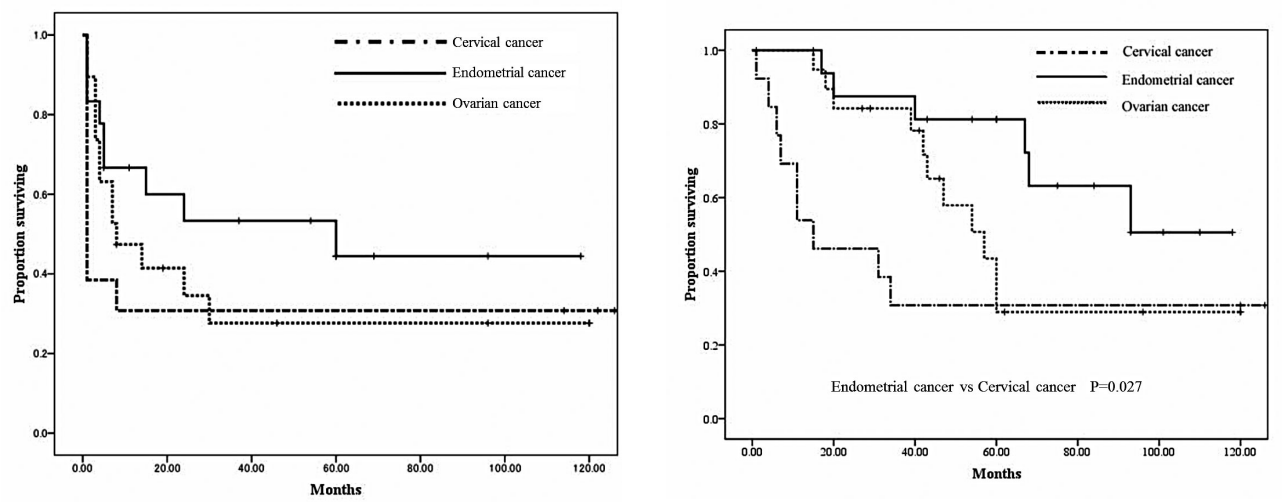


Figure 1. — A) Progression-free survival of each cancer type after initial surgery for recurrent tumor. B) Overall survival of each cancer type after initial surgery for recurrent tumor.

PFS and five-year PFS after initial surgery for recurrent tumor were 74 months and 46%, respectively, and median OS and five-year OS after initial surgery for recurrent tumor were 100 months and 68%, respectively (Figures 2C, D). In the incomplete surgery group, median PFS and five-year PFS after initial surgery for recurrent tumor were one month and 0%, respectively, and median OS and five-year OS were 30 months and 0%, respectively (Figures 2C, D). In ovarian cancer, complete surgery, complications, and bleeding exceeding 1,000 mL were associated with improved PFS, and complete surgery and bleeding exceeding 1,000 mL were associated with improved OS. In the complete surgery group with ovarian cancer, median PFS and five-year PFS after initial surgery for recurrent tumor were 14 months and 30%, respectively, and median OS and five-year OS were 60 months and 32%, respectively (Figures 2E, F). In the incomplete surgery group, median PFS and five-year PFS after initial surgery for recurrent tumor were four months and 0%, respectively, and median OS and five-year OS were 20 months and 0%, respectively. On multivariate analysis, there were no significant differences among these variables in cervical and ovarian cancers, but there were significant differences in complete surgery (PFS, hazard ratio [HR] 38.117, 95%CI 1.861-780.729, $p = 0.015$ and OS, HR 41.412, 95%CI 1.629-1053.024, $p = 0.024$) and the number of recurrent tumors (PFS, HR 38.117, 95%CI 1.861-780.729, $p = 0.015$ and OS, HR 41.412, 95%CI 1.629-1053.024, $p = 0.024$) in endometrial cancer.

PFS and OS for all cancer types together were evaluated, and on univariate analysis, there was a significant difference in OS between endometrial carcinoma and cervical carcinoma (Figure 1B). However, on multivariate analysis, there was no significant difference among cancer types, but there were significant differences in complete surgery (HR 4.738, 95% CI 1.341-16.745, $p = 0.016$) and the number of recurrent tumors (HR 6.997, 95% CI 2.481-19.735, $p = 0.000$). Cox regression analysis showed that the number of tumors was significantly correlated with complete surgery (HR 6.974, 95% CI 1.146-42.429, $p = 0.035$), but cancer type was not.

## Discussion

The treatment strategy for recurrent solid tumors differs for each cancer type, but it is evident that it is actually difficult to achieve complete cure by any therapy. When a recurrent tumor affects a local area, surgical treatment or radiation therapy is chosen, but if it spreads into a distant area, chemotherapy is administered because it is then considered a systemic disease. For gynecological oncologists, cervical, endometrial, and ovarian cancers are common cancer types, and the initial treatment strategy has been established recently, but strategies for recurrent disease differ by institution. Surgical treatment is a fundamental option for primary disease with these three cancers, but for recurrent disease, surgery is rarely chosen because recurrent disease appears to be systemic disease, but there is no solid evidence for this. Some studies have shown that surgical treatment is a good therapeutic option for recurrent gynecological cancer and achieves a good prognosis [11-18]. The decision to treat recurrent tumors by surgery depends on the characteristics of each cancer type, and some criteria, especially in ovarian cancer, have been reported using parameters such as performance status, tumor markers, the results of primary surgery, and ascites [17,18]. The most important prognostic factor for recurrent tumor after surgical treatment is no residual disease [14-18], so that it is important to perform a precise preoperative evaluation of

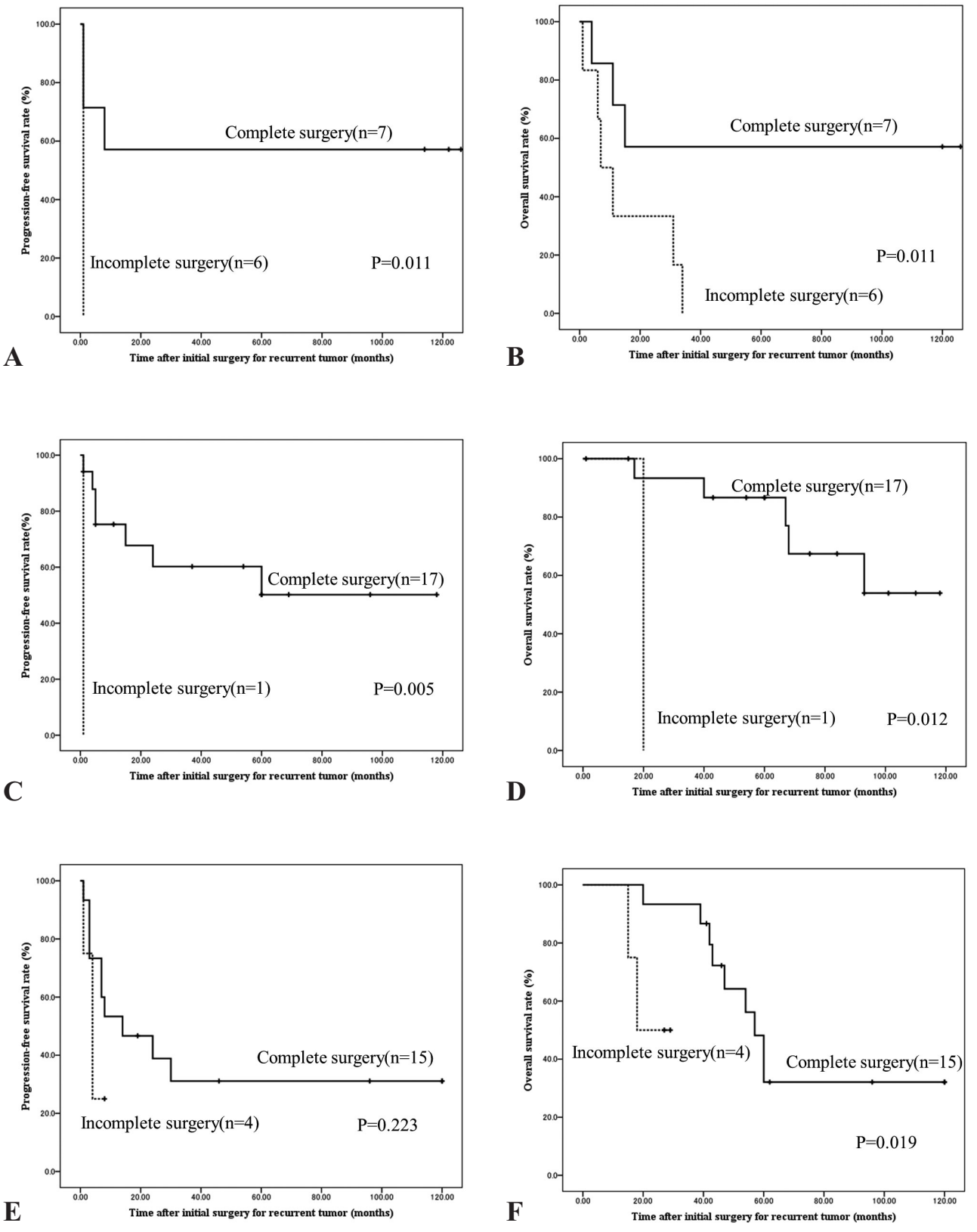


Figure 2. — Survival by residual disease after initial surgery for recurrent tumor. A) Progression-free survival of cervical cancer. B) Overall survival of cervical cancer. C) Progression-free survival of endometrial cancer. D) Overall survival of endometrial cancer. E) Progression-free survival of ovarian cancer. F) Overall survival of ovarian cancer.

resectability.

In the present study, as for surgical results, among the three cancer types, the complete resection rate was the best for endometrial cancer and the worst for cervical cancer. CT and PET-CT are the usual diagnostic modalities to define not only recurrence, but also resectability. In the present study, the PPV of preoperative assessment of resectability was different for each cancer type, and this was likely dependent on the characteristics of each cancer type. For example, 9/13 (69.2%) cervical cancer patients had recurrent tumor in the irradiated field, which made it difficult to remove the tumor because of fibrosis or adhesions. Popovich *et al.* reported that CT and MRI can be helpful in assessing the presence of lateral pelvic wall invasion or liver metastases of cervical cancer, but the major limitation of CT and MRI is their inability to assess minimally enlarged nodes to detect microscopic peritoneal disease and to distinguish fibrosis from tumor in recurrent disease; furthermore, the fact that most patients have usually received extensive radiation makes distinguishing radiation fibrosis from malignant tumor extremely difficult [19]. Unlike in cervical cancer, the complete resection rate of endometrial cancer was better, and it is estimated that preoperative evaluation by CT for recurrent endometrial cancer is the most reliable, and patient selection was actually good in the present study. Ren *et al.* reported that careful selection of patients is important due to the complications of salvage cytoreductive surgery. They attempted to predict optimal cytoreduction, and associated factors with optimal cytoreduction in recurrent endometrial cancer were identified by logistic regression analysis. On univariate analysis, age, progression-free interval (PFI), the size of the largest recurrent tumors, the site of recurrence, and multiplicity of recurrence were associated with optimal cytoreduction, which indicates that patients with younger age, longer PFI, smaller tumor size, recurrence site not in the retroperitoneal region, and single recurrence are more likely to achieve optimal cytoreduction. However, on multivariate analysis, only age, the size of the largest recurrent tumors, and multiplicity of recurrence were associated with optimal cytoreduction [19]. On the other hand, the complete resection rate of recurrent ovarian cancer in this study was 78.9%. Some scores that can be used to identify patients eligible for surgery have been reported [17, 18]. The AGO DESKTOP OVAR trial identified preoperative predictors of complete surgery: performance status (PS), history of complete resection during the first intervention, and absence of ascites of more than 500 mL [17]. Tian *et al.* identified a model to predict complete resection in REOC that consisted of the DESKTOP score, along with the disease-free interval, CA125 rate, and initial disease stage [18]; sensitivity was 80.4% and specificity was 52.6% [17, 18]. The number of cases in the present study was small, but evaluation of resectability of REOV by CT and PET-CT in this study was similar to these two scores. Thus, precise evaluation of recurrent ovarian cancer for resectability by CT or PET-CT appears to be equivalent to these reported scoring systems.

PFS and OS after surgery for recurrent gynecological cancer have recently been reported [11-13]. In cervical cancer, if recurrent tumor is in the irradiated pelvic field, pelvic exenteration (PE) has been performed. If the patients are selected appropriately, five-year OS is reported to be 34-50%. With respect to lung metastasis, resection of a solitary tumor achieves a good prognosis [20]. In the present univariate analysis for cervical cancer, the number of recurrent tumors, complete surgery, and complications affected PFS and OS. On the other hand, the site of recurrence and a history of irradiation did not affect the prognosis. However, the multivariate analysis did not show any factors that affected PFS and OS due to the small number of cases. The Kaplan-Meier curve in cervical cancer showed that the curves of PFS and OS with complete surgery were quite similar, and if patients survived without recurrence for 20 months, they survived for quite a long time. Unlike endometrial and ovarian cancers, complete surgery of recurrent cervical cancer, except for pelvic exenteration, has not been well discussed, so that the present result suggests that complete resection for recurrent cervical cancer is valuable.

In endometrial cancer, surgical treatment for recurrent tumor has recently been discussed. Some studies reported the efficacy of surgical treatment for recurrent endometrial cancer, and optimal reduction and isolated recurrence were significant prognostic factors, similar to ovarian cancer. Papadia *et al.* reported the outcomes of 64 surgical resections in patients with recurrent endometrial cancer [16]. In their study, optimal cytoreduction was achieved in 65.6%. Histology and optimal residual disease were associated with better OS. They reported that five-year PFS was 42% and 19% in optimally and suboptimally cytoreduced patients, respectively, and five-year OS was 60% and 30% in optimally and suboptimally cytoreduced patients, respectively. They mentioned only a few series of secondary cytoreduction in recurrent endometrial cancer that were related to patients' characteristics, such as older age, obesity, and multiple comorbidities, which make surgical management difficult [16]. It is important to note that the endometrial cancer patients were the oldest patients, but complications and the bleeding rate were lower in the present study than in previous reports [16]. Thus, the factors associated with adverse operative events are associated with other factors such as invasiveness, location, and history of radiotherapy. The high resectability rate in the present study seems to be associated with the difference in adjuvant therapy between Japan and other countries. Japanese institutions have chosen chemotherapy for postoperative adjuvant therapy or for advanced or recurrent endometrial cancer [21], but the US and European countries have used radiation therapy as adjuvant therapy until GOG122 was reported. GOG 122 demonstrated the superiority of systemic chemotherapy

over whole abdominal radiotherapy after optimal surgery [22], so that surgical treatment for recurrent endometrial cancer will be much more acceptable in the future.

Among the three cancer types in the present study, ovarian cancer had the worst PFS and OS; the survival curve for PFS was similar to that of cervical cancer, but that of OS appeared better than that of cervical cancer. This indicates that the difference in OS in the present study was caused by fewer reliable chemotherapies for recurrent cervical cancer than for ovarian cancer, so that many cervical and ovarian cancer patients have repeated recurrences after surgical treatment for recurrence, and some ovarian cancer patients who received chemotherapy could survive a long time with disease. In the present study, 9/19 (47.4%) ovarian cancers were first recurrences, so that half of the recurrent patients had already been treated by some kind of chemotherapy. In the reported series of surgery for recurrent ovarian cancer, the timing of surgery was defined as first recurrence, so treatment was challenging, because 10/19 (52.6%) patients were platinum-resistant. Two of the patients achieved quite a long survival; therefore, surgical treatment for some patients with platinum resistance may contribute to long survival.

In the present study, when survival of these three cancers together was analyzed, five-year OS was significantly different between endometrial and cervical cancer. However, on multivariate analysis, cancer type was not associated with PFS and OS, and complete surgery and number of recurrences were associated with both PFS and OS. This shows that the most important factor in surgery for recurrent gynecological cancer is complete surgery, and it is not dependent on the cancer type. Thus, complete surgery and the modality to assess the resectability of recurrent tumor before surgery are fundamental and very important.

In conclusion, surgical treatment for recurrent gynecological cancer is an acceptable and valuable therapeutic option if the tumor is considered to be completely resectable on radiologic examination. It is important to establish some criteria for selecting candidates for surgical treatment for recurrent gynecological cancer, especially for cervical cancer. This study was retrospective, and the number of patients was small, so that there are several limitations that might have introduced a patient selection bias. To identify patients who can benefit from surgical treatment for recurrent gynecological cancer, a study with a larger sample or a randomized, controlled study is needed.

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