의학석사 학위논문

Optimal cytoreduction and platinum-free interval affecting the duration of bevacizumab-based maintenance therapy and prognosis in the first platinum-sensitive recurrence of ovarian cancer

백금 민감성 재발성 난소암 환자에서 베바시주맙 유지 치료 기간과 예후를 예측할 수 있는 인자에 대한 후향적 연구

2022년 8월

서울대학교 대학원

의학과 산부인과전공

오 수 현

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이 논문을 의학석사 학위논문으로 제출함

2022년 4월

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오수현의 의학석사 학위논문을 인준함

2022년 7월

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Abstract

Optimal cytoreduction and platinum-free interval affecting the duration of bevacizumab-based maintenance therapy and prognosis in the first platinum-sensitive recurrence of ovarian cancer

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Background: Even though bevacizumab-based maintenance therapy (BMT) reportedly improved overall survival in the first platinum-sensitive recurrence of ovarian cancer, there was a lack of factors for predicting how long it will last. Thus, we investigated factors affecting the duration of the maintenance therapy and their effect on the prognosis of the disease.

Methods: We included patients diagnosed with the first platinum-sensitive recurrence of ovarian cancer in two tertiary centers from January 2015 till August 2021. All patients received six cycles of paclitaxel-carboplatin-bevacizumab, followed by BMT. We retrospectively collected data such as age, histologic types, status of BRCA mutation, platinum-free intervals (PFI), extent of primary and secondary cytoreduction, presence of extra-abdominal disease, number of recur lesions, duration of BMT, progression-free survival (PFS) and cancer-specific survival (CSS) after the first recurrence.

Results: A total of 103 patients were included, and the median cycles of BMT was 13 (range, 1-108). Among them, 74 (71.8%) and 22 (21.4%) patients underwent optimal primary and secondary cytoreduction, respectively. PFI

>12 months was factors for predicting 13 or more cycles of BMT (adjusted odds ratio, 3.770; 95% confidence intervals [CIs], 1.654–8.595), and improving both PFS and CSS (adjusted hazard ratios [HRs], 0.474 and 0.149; 95% CIs, 0.282–0.797 and 0.036–0.610). Additionally, the higher number of recur lesions was associated with poor PFS and CSS (adjusted HRs, 3.240 and 14.880; 95% CIs, 1.509–6.954 and 1.047–211.43).

Conclusion: PFI > 12 months potentially predicted 13 or more cycles of BMT. PFI > 12 months and the lower number of recur lesions were related to improved survival in the first platinum–sensitive recurrence of ovarian cancer.

Keywords: ovarian cancer, bevacizumab, maintenance therapy, platinum–free interval, number of lesions

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Chapter 1. Introduction

Ovarian cancer is the second most common female malignancy and the leading cause of death due to female malignancy in USA. [1] In Korea, the incidence of ovarian cancer reached 2,630 in 2016. [2] Despite the initial aggressive treatment, 22% of patients experience recurrence within six months from the last platinum-based chemotherapy, and more than two-thirds of the patients relapse within one year. [3] Platinum-sensitive ovarian cancer refers to recurrence after six months from completion of platinum chemotherapy. The standard therapy of platinum-sensitive disease is re-administration of platinum-based chemotherapy. After cytotoxic chemotherapy, maintenance therapy such as angiogenic inhibitors or poly (ADP ribose) polymerase (PARP) inhibitors is recommended to delay recurrence.

Bevacizumab, monoclonal antibody that inhibits vascular endothelial growth factor, was recognized for the treatment of platinum-sensitive recurrence based on two randomized controlled trials. First, OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease) trial showed significant increase in progression-free survival (PFS) in patients who received gemcitabine and carboplatin with bevacizumab than patients with standard chemotherapy alone. However, overall survival (OS) remained similar. [4,5] According to GOG-0213 (NRG Oncology/Gynecologic Oncology Group study GOG-0213), significant improvement in PFS and OS was noted in patients in paclitaxel, carboplatin and bevacizumab group compared to chemotherapy without bevacizumab group. [6]

However, there are few studies to investigate factors to predict efficacy of bevacizumab in platinum-sensitive recurrent ovarian cancer. A retrospective study analyzed predictive value of Cyclin E1(CCNE1) expression and reported that patients with platinum-free interval (PFI) of 6 to 12 months and overexpression of CCNE1 showed best response to

bevacizumab. [7] In addition, subgroup analysis of GOG-0213 and OCEANS trials suggested patients with PFI of 6-12 months had greater benefit from bevacizumab than those over 12 months. However, these studies compared platinum-based chemotherapy with bevacizumab to chemotherapy without it. Evidence is limited regarding factors associated with the duration of bevacizumab-based maintenance therapy (BMT). Therefore, to search for the predictive factors and analyze their influences on the prognosis, we performed this study to predict long-term use of BMT in the first platinum-sensitive recurrent ovarian cancer.

Chapter 2. Methods

2.1. Patients

Patients over 18 years of age were included if they received platinum-based chemotherapy with bevacizumab and BMT for platinum-sensitive recurrence of ovarian cancer from January 2015 to August 2021 in two tertiary centers. We excluded the patients who have not started BMT so far. The study protocol was approved by the institutional review board of the two institutions. (No, 2203-096-1305 and GCIRB2022-077)

The included patients underwent six cycles of paclitaxel (175mg/m2), carboplatin (area under the curve 5), and bevacizumab (15mg/kg) every three weeks. Then, they continued BMT until disease progression or serious toxicities were identified. In case of secondary cytoreduction, bevacizumab was administered from the second cycle of the chemotherapy. The treatment response was evaluated every three cycles by cancer antigen 125 (CA125) Gynecologic Cancer Intergroup (GCIG) criteria or Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

2.2. Clinical data

The medical records were reviewed retrospectively and following items were collected: age at recurrence, histologic types, status of BRCA mutation, PFI, presence of extra-abdominal disease, number of recur lesions, extent of primary and secondary cytoreduction, duration of BMT, date of disease progression, death, or last follow-up. The optimal cytoreduction was achieved when residual tumor was less than 1cm. PFS and cancer-specific survival (CSS) were defined respectively as the interval from the date of first recurrence to date of the diagnosis of second recurrence and death due to the disease or last follow-up.

To find factors affecting the duration of BMT, we calculated the median number of cycles of BMT in included patients. Total 103 patients were included, and they received median 13 times of maintenance treatment. (range, 1-108) Based on 13 cycles of BMT, patients were divided into two groups. Patients were excluded who started BMT recently and received less than 13 cycles.

2.3. Statistical analysis

The frequencies of patients' clinicopathologic variables were expressed as number of cases. Baseline characteristics of two groups were compared by Pearson's chi-squared test or Fisher's exact test. We adopted logistic regression to calculate associations between the duration of BMT and each variable. The cox proportional hazards model was used to determine prognostic value of the variables. We also performed subgroup analysis of patients except those who discontinued BMT for the reasons apart from progression. Statistical analysis was performed with SPSS Statistical Software (Version 22.0, SPSS Inc., Chicago, IL). The results were statistically significant if p value was less than 0.05.

Chapter 3. Results

We identified 112 patients who received BMT for platinum-sensitive recurrence of ovarian cancer. Nine patients were excluded in whom maintenance therapy has been administered less than 13 cycles and continuing the treatment. Remained 103 patients were divided into two groups, so that short-term BMT group included 49 patients who underwent less than 13 cycles of BMT and long-term BMT group consisted of 54 patients with at least 13 cycles of BMT. Table 1 presents patients' baseline characteristics. Patients were similar in age at recurrence, histologic type, BRCA mutational status and extent of primary cytoreduction. On the other hand, more patients in long-term BMT group had PFI of more than 12 months than short-term BMT group. (38 and 20 patients, respectively, p=0.002) The optimal secondary cytoreduction was accomplished in 22 patients (21.4%), and 18 of them were long-term BMT group. The imaging findings showed higher number of recur lesions in short-term BMT group. Complete or partial response was observed in 53 patients (98.2%) in long-term BMT group, while 41 patients (83.7%) showed objective response in short-term BMT group. ($p < 0.001$) Total 81 patients stopped BMT for reasons including progression, toxicities, patients' request, and loss to follow-up. More patients discontinued it due to progression in short-term BMT group than in long-term BMT group. (34 and 22 patients, $p < 0.001$)

Table 2 displays factors associated with continuation of BMT beyond 13 cycles. PFI > 12 months influenced the duration of BMT significantly. (adjusted odds ratios [aORs], 3.770; 95% confidence intervals [CIs], 1.654-8.595) Subgroup analysis showed longer duration of BMT was associated with PFI > 12 months (aORs; 6.995; 95% CIs 2.418–20.237) and lower number of recur lesions (aORs; 0.259 and 0.092; 95% CIs 0.073-0.911 and 0.013-0.639) (Table 2)

After second line treatment, recurrence was observed in 70 patients. Improved survival was observed in patients of PFI > 12 months and fewer

recur lesions. Table 3 displays results of multivariate analysis. PFI > 12 months and number of recur lesions were independent prognostic factors for PFS (adjusted hazard ratio [HRs], 0.474 and 3.240; 95% CIs, 0.282–0.797 and 1.509–6.954) The significant prognostic effects were maintained in subgroup analysis.

Total 12 patients were died of the disease. (8 and 4 patients in short-term and long-term BMT group) A 5-year CSS rates were 61.1% and 82.2% respectively in short-term and long-term BMT group. (p=0.005) Figure 2 shows survival curve in all patients and pre-defined subgroup, according to histology, PFI, and number of recur lesions. PFI and number of recur lesions were important prognostic factor for CSS. Based on the results of multivariate analysis, PFI > 12 months was significant for improved CSS. (adjusted HRs, 0.149; 95% CIs, 0.036–0.610), while histologic types other than high grade serous carcinoma and multiple recur lesions were poor prognostic factor. (adjusted HRs, 5.156 and 14.880; 95% CIs, 1.310–20.295 and 1.047–211.43) Consistent results were observed in subgroup analysis. (Table 4)

Chapter 4. Discussion

This retrospective study was conducted to identify predictive factors for the duration of BMT and their prognostic impact on survival in the first platinum-sensitive recurrent ovarian cancer. PFI > 12 months showed significant association with extended use of BMT and number of recur lesions were also possibly associated with it. Furthermore, these factors were potential prognostic factors for PFS and CSS.

We found median 13 times of BMT have been provided to the patients included in this study. The number of cycles of BMT is comparable to previous studies. First, in GOG-0213, the median number of BMT was 16. (range, 1–111) The patients of OCEANS trial were administered median 12

cycles of maintenance therapy. (range, 1–43) In addition, PFS and CSS were significantly improved in patients who received 13 or more cycles of BMT in this study, therefore, we decided to classify patients into two groups according to the median number of BMT.

PFI is recognized as an important prognostic factor that correlates with possibility of responses to subsequent treatment. The patients with longer PFI have greater chance to show response to platinum chemotherapy. Also, the association of PFI with survival was demonstrated in the literatures. [8,9] Wu et al retrospectively analyzed outcomes of BMT in women with relapsed ovarian cancer. [10] When survival rates were compared according to PFI, results showed notable survival gain in patients with a longer PFI. Similarly, PFI was a statistically significant factor for continuation of BMT and survival in our analysis. On the other hand, previous studies reported contrary results to this study. Patients with PFI of 6–12 months had a greater benefit from BMT than those with a longer PFI. [4,6,7] Possible explanation A study performed an exploratory analysis of data from AURELIA (Avastin Use in Platinum–Resistant Epithelial Ovarian Cancer) to compare treatment outcomes between primary platinum resistance (PPR) and secondary platinum resistance (SPR). [11] PPR and SPR were defined as platinum resistant recurrence after first– and second–line platinum–based chemotherapy. Improved PFS and OS were observed in patients of SPR group, compared to PPR group. (median 10.2 versus 5.6 months, $p < 0.001$; median 22.2 versus 13.7 months, $p < 0.001$) Multivariate analysis also demonstrated that SPR and PFI were prognostic factor for survival. Longer PFI implies that patients have less aggressive tumor and the time to progression appeared to be important to determine efficacy of bevacizumab and prognosis. The predictive role of PFI for BMT should be investigated further.

The studies of patients with platinum–sensitive recurrent ovarian cancer found that the increasing number of recurrence sites had prognostic

significance for poor survival. A retrospective analysis of 153 patients demonstrated progressive decrease in median survival time as the number of lesions increased. (60, 42 and 28 months in patients with a single site, multiple sites, and carcinomatosis, respectively) [12] Furthermore, according to multivariate analysis in other retrospective analysis, the number of lesions was independent prognostic factor of PFS and overall survival. [13,14] It was also significant predictor for survival and BMT in this study, while other imaging findings, such as presence of extra-abdominal lesion failed to show important association.

This study has several limitations. Due to its retrospective nature, it is difficult to generalize the results to a larger population. There is also possibility of errors or omissions in the medical records, leading to documentation bias. Besides, we divided the patients into two groups based on 13 cycles of BMT. There is no clear definition that describe long-term and short-term use of maintenance therapy. The definition we adopted should be validated in a general population.

In conclusion, PFI > 12 months were significant predictive factors of continuation of BMT and better survival. The number of recurrence sites was also suggested to be associated with BMT and survival. This result could help physician to find out which patients can benefit from BMT.

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요약 (국문초록)

백금 민감성 재발성 난소암 환자에서 베바시주맙 유지 치료 기간과 예후를 예측할 수 있는 인자에 대한 후향적 연구

백금 민감성 재발성 난소암에서 베바시주맙을 이용한 유지 치료가 생존기간을 연장시키는 데에 기여하였다는 사실이 여러 연구를 통해 알려졌다. 그러나 베바시주맙 유지 치료 기간을 예측할 수 있는 인자에 대한 연구는 부족하다. 그리하여 이번 연구를 통해 베바시주맙 유지 요법 기간을 예측할 수 있는 인자들과 그 인자들이 재발성 난소암의 예후에 미치는 영향을 분석하고자 한다.

2015년 1월부터 2021년 8월까지 서울대병원과 가천의대 길병원 두 곳에서 백금 민감성 재발성 난소암으로 진단받은 환자들을 연구에 포함하였다. 환자들에게는 모두 6번의 파클리탁셀, 카보플라틴 및 베바시주맙 병합 요법을 투여하였으며 이후 베바시주맙 유지 치료를 시행하였다. 의무 기록을 후향적으로 분석하여 나이, 조직학적 유형, BRCA 변이 유무, 무백금기간, 일차 및 이차 종양감축술, 복강 외 전이 여부, 재발된 부위의 개수, 유지치료 기간, 무진행생존기간, 난소암 특이 생존기간 등의 정보를 수집하였다.

총 103명의 환자를 분석하였고 환자들에게 투여한 베바시주맙 유지 치료 횟수의 중앙값은 13회였다. (투여 횟수 범위는 1-108회였다.) 환자들 중 74명 (71.8%)와 22명 (21.4%)에서 적절한 일차 및 이차 종양감축술이 각각 이루어졌다. 다변량 분석을 통해 무백금기간이 12개월을 초과한 경우는 13회 이상의 베바시주맙 유지 치료와 유의한 관계가 있음을 확인하였다. (보정된 교차비는 3.770. 95% 신뢰구간은 1.654-8.595이다.) 또한 무백금기간이 12개월을 초과한 환자의 경우 무진행생존기간 및 난소암 특이 생존기간이 연장되었다. (보정된 위험비는 0.474과 0.149이고, 95% 신뢰구간은 각각 0.282-0.797과 0.036-0.610이다.) 또한 재발된 부위의 개수가 많을수록 무진행생존기간과 난소암 특이생존기간이 단축되었다. (보정된 위험비는 3.240과 14.880이고, 95% 신뢰구간은 1.509-6.954와 1.047-211.43이다.)

결론적으로 백금 민감성 재발성 난소암 환자에서 12개월을 넘는 무백금기간은 베바시주맙 유지치료의 기간을 예측할 수 있는 인자이며 생존기간의 연장과도 유의한 관계가 있다. 또한 재발된 부위의 개수도 생존기간을 예측하는데 있어 중요한 인자로 생각된다.

Table 1. Characteristics of 103 patients with first platinum-sensitive recurrence of ovarian cancer

Characteristics	Cycles of maintenance bevacizumab		*p* value
	< 13 (n=49, %)	≥ 13 (n=54, %)	
Age at recurrence (y)			0.080
< 57	17 (37.8)	28 (62.2)	
≥ 57	32 (55.2)	26 (44.8)	
Histology			0.460
HGSC	37 (75.5)	44 (81.5)	
Non-HGSC	12 (24.5)	10 (18.5)	
Status of BRCA mutation			0.708
Wild	34 (69,4)	39 (72.2)	
BRCA1 mutation	6 (12.2)	8 (14.8)	
BRCA2 mutation	3 (6.1)	1 (1.9)	
Unknown	6 (12.2)	6 (11.1)	
Primary cytoreduction			0.727
Optimal	36 (73.5)	38 (70.4)	
Suboptimal	13 (26.5)	16 (29.6)	
PFI (mons)			0.002
6-12	29 (59.2)	15 (27.8)	
> 12	20 (40.8)	39 (72.2)	
Secondary cytoreduction			0.003
Optimal	4 (8.2)	18 (33.3)	

Suboptimal	4 (8.2)	3 (5.6)	
Not performed	41 (83.7)	33 (61.1)	
Extra-abdominal lesion			0.924
No	34 (69.4)	37 (68.5)	
Yes	15 (30.6)	17 (31.5)	
No. of recur lesions			0.010
1-3	11 (22.4)	25 (46.3)	
4-19	26 (53.1)	25 (46.3)	
≥ 20	12 (24.5)	4 (7.4)	
Tumor response			< 0.001
Complete response	10 (20.4)	30 (55.6)	
Partial response	31 (63.3)	23 (42.6)	
Stable disease	8 (16.3)	1 (1.9)	
Reasons for stopping			< 0.001
PD	34 (69.4)	22 (40.7)	
Other than PD*	15 (30.7)	10 (18.6)	

Abbreviation: HGSC, high-grade serous carcinoma; PFI, platinum-free interval; PD, progressive disease

*: reasons including toxicities, patients' request, or loss to follow-up

Table 2. Factors affecting 13 or more cycles of maintenance bevacizumab for the first platinum-sensitive recurrence of ovarian cancer

Characteristics	OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value
All patients						
Age ≥ 57y	0.574	0.236 - 1.396	0.221	-	-	-
Non-HGSC	0.374	0.120 - 1.160	0.089	-	-	-
BRCA 1 or 2 mutation	0.638	0.200 - 2.041	0.449	-	-	-
Suboptimal cytoreduction after primary disease	0.871	0.321 - 2.361	0.786	-	-	-
PFI > 12 mons	3.745	1.434 - 9.783	0.007	3.770	1.654 - 8.595	0.002
Extra-abdominal metastasis	1.593	0.617 - 4.110	0.336	-	-	-
No. of recur lesions						
4-19	0.560	0.208 - 1.509	0.251	-	-	-
≥ 20	0.236	0.052 - 1.062	0.060	-	-	-
Excepts for patients who discontinued due to reasons other than PD						
Age ≥ 57y	0.428	0.134 - 1.368	0.152	-	-	-
Non-HGSC	0.318	0.069 - 1.469	0.142	-	-	-

BRCA 1 or 2 mutation	0.345	0.080 – 1.481	0.152	–	–	–
Suboptimal cytoreduction after primary disease	0.584	0.149 – 2.292	0.440	–	–	–
PFI > 12 mons	12.613	3.444 – 46.192	<0.001	6.995	2.418 – 20.237	<0.001
Extra-abdominal metastasis	1.754	0.544 – 5.659	0.347	–	–	–
No. of recur lesions						
4-19	0.256	0.065 – 1.010	0.052	0.259	0.073 – 0.911	0.035
≥ 20	0.083	0.010 – 0.673	0.020	0.092	0.013 – 0.639	0.016

Abbreviation: OR, odds ratio; CI, confidence interval; HGSC, high-grade serous carcinoma; PFI, platinum-free interval; PD, progressive disease

Table 3. Factors affecting progression-free survival after the first recurrence

Characteristics	HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
All patients						
Age ≥ 57y	1.160	0.688 - 1.958	0.577	-	-	-
Non-HGSC	1.089	0.561 - 2.112	0.801	-	-	-
BRCA 1 or 2 mutation	1.621	0.840 - 3.128	0.150	-	-	-
Suboptimal cytoreduction after primary disease	1.048	0.611 - 1.797	0.865	-	-	-
PFI > 12 mons	0.455	0.260 - 0.797	0.006	0.474	0.282 - 0.797	0.005
Extra-abdominal metastasis	0.956	0.559 - 1.633	0.868	-	-	-
No. of recur lesions						
4-19	2.955	1.562 - 5.591	0.001	2.796	1.550 - 5.045	0.001
≥ 20	3.411	1.509 - 6.954	0.003	3.240	1.509 - 6.954	0.003
Excepts for patients who discontinued due to reasons other than PD						
Age ≥ 57y	1.194	0.682 - 2.088	0.535	-	-	-
Non-HGSC	1.079	0.502 - 2.322	0.842	-	-	-

BRCA 1 or 2 mutation	1.386	0.672 – 2.859	0.377	–	–	–
Suboptimal cytoreduction after primary disease	1.224	0.653 – 2.294	0.529	–	–	–
PFI > 12 mons	0.385	0.209 – 0.710	0.002	0.404	0.227 – 0.719	0.002
Extra–abdominal metastasis	0.882	0.483 – 1.607	0.681	–	–	–
No. of recur lesions						
4–19	2.870	1.347 – 6.112	0.006	2.720	1.352 – 5.476	0.005
≥ 20	5.392	2.001 – 14.532	0.001	4.776	1.883 – 12.118	0.001

Abbreviation: HR, hazard ratio; CI, confidence interval; HGSC, high–grade serous carcinoma; PFI, platinum–free interval; PD, progressive disease

Table 4. Factors affecting cancer-specific survival after the first recurrence

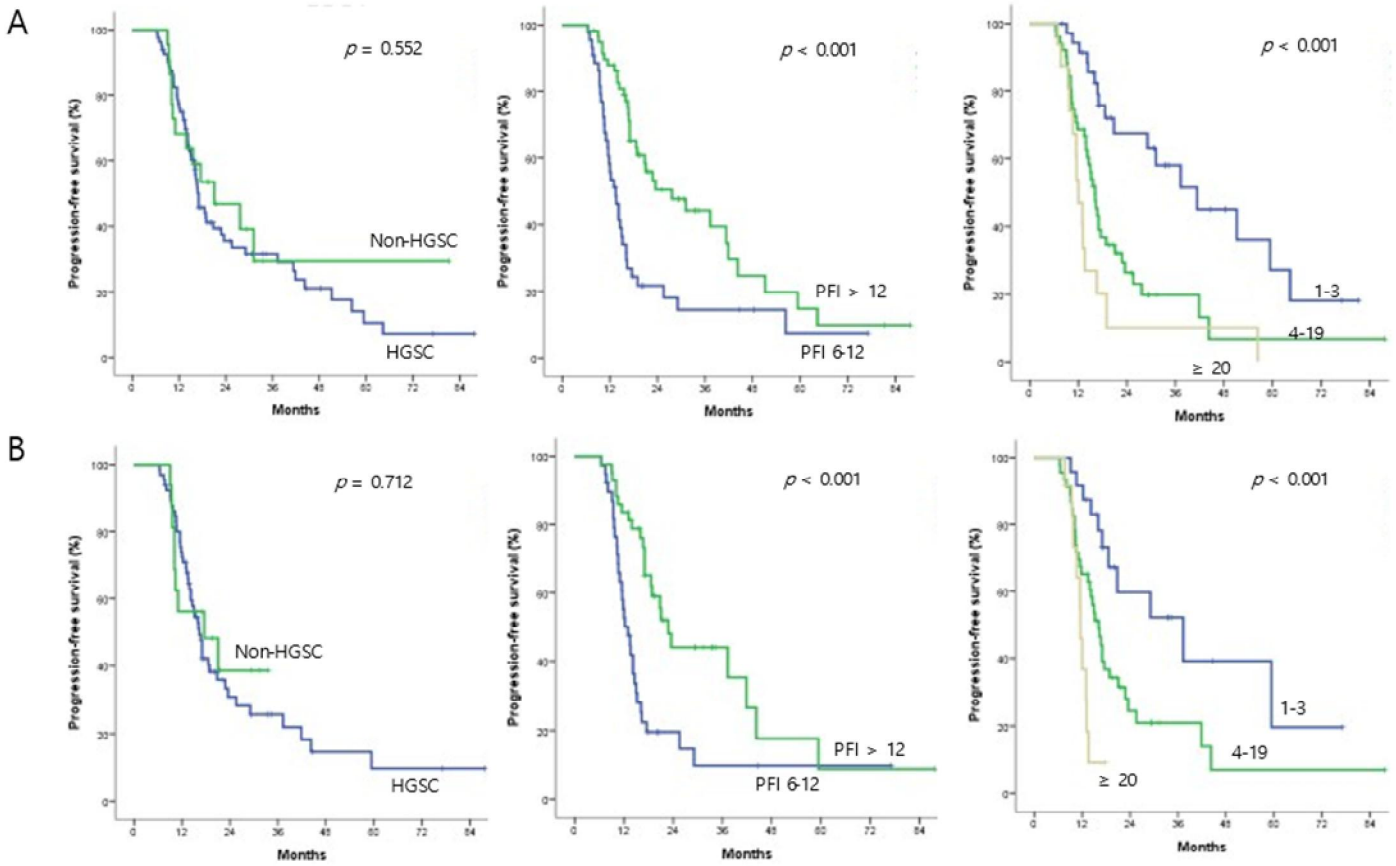
Characteristics	HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
All patients						
Age ≥ 57y	0.763	0.211 - 2.754	0.679	-	-	-
Non-HGSC	6.653	1.491 - 29.680	0.013	5.156	1.310 - 20.295	0.019
BRCA 1 or 2 mutation	5.043	0.649 - 39.165	0.122	6.578	0.966 - 44.778	0.054
Suboptimal cytoreduction after primary disease	1.844	0.478 - 7.122	0.375	-	-	-
PFI > 12 mons	0.140	0.034 - 0.575	0.006	0.149	0.036 - 0.610	0.008
Extra-abdominal metastasis	1.575	0.401 - 6.182	0.515	-	-	-
No. of recur lesions						
4-19	13.012	0.925 - 183.05	0.057	12.641	1.047 - 152.63	0.046
≥ 20	17.304	1.105 - 271.09	0.042	14.880	1.047 - 211.43	0.046

Excepts for patients who discontinued due to reasons other than PD

Age ≥ 57y	0.952	0.260 – 3.487	0.941	–	–	–
Non-HGSC	6.371	1.331 – 30.502	0.020	5.718	1.407 – 23.247	0.015
BRCA 1 or 2 mutation	2.834	0.329 – 24.432	0.343	–	–	–
Suboptimal cytoreduction after primary disease	1.822	0.453 – 7.319	0.398	–	–	–
PFI > 12 mons	0.190	0.046 – 0.779	0.021	0.212	0.054 – 0.836	0.027
Extra-abdominal metastasis	1.181	0.279 – 4.997	0.821	–	–	–
No. of recur lesions						
4-19	7.424	0.521 – 105.87	0.139	3.832	0.444 – 33.092	0.222
≥ 20	32.514	1.654 – 639.25	0.022	22.082	1.508 – 323.28	0.024

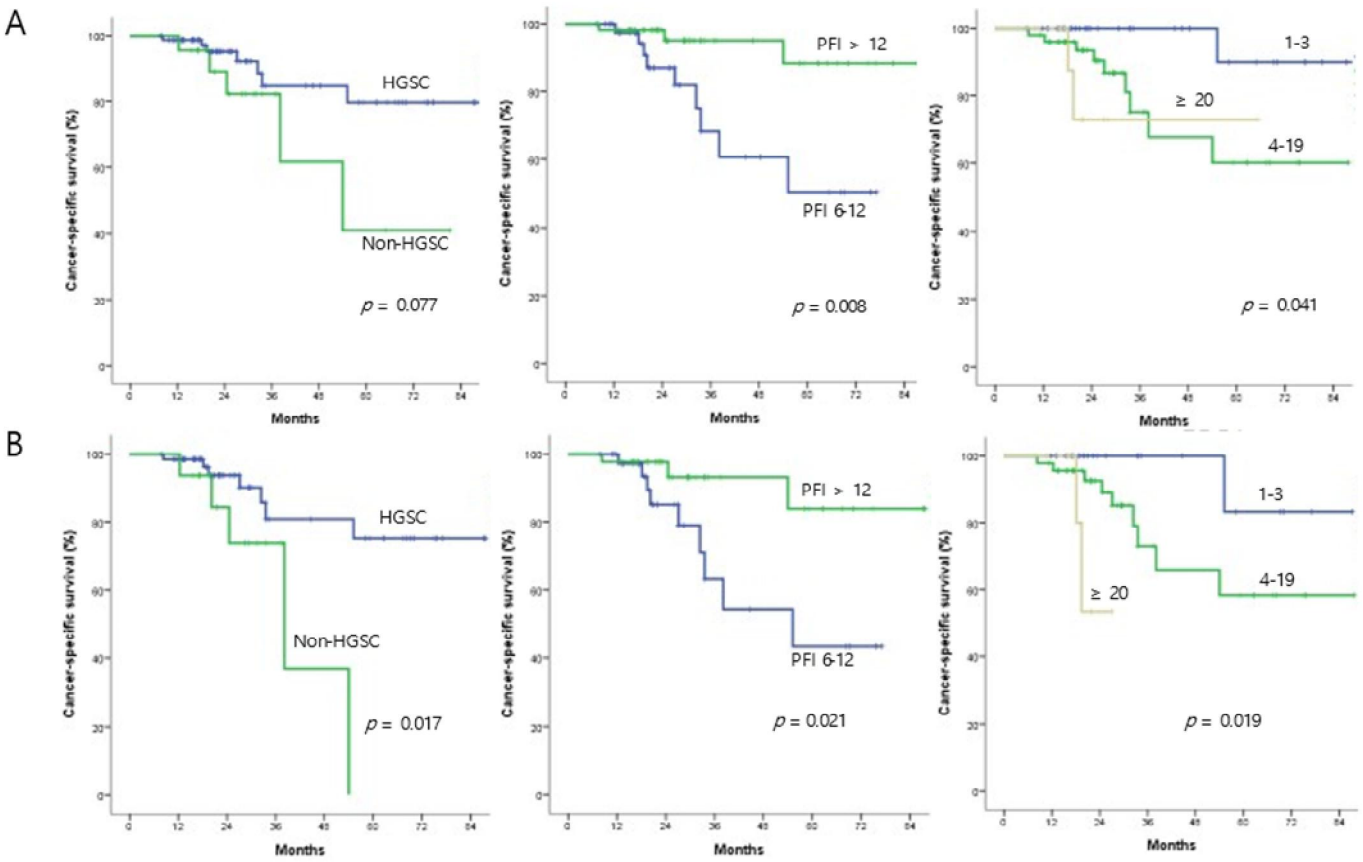
Abbreviation: HR, hazard ratio; CI, confidence interval; HGSC, high-grade serous carcinoma; PFI, platinum-free interval; PD, progressive disease

Figure 1. PFS in (A) all patients and (B) patients except for those who discontinued BMT due to reasons other than PD according to histologic type, PFI, and number of recur lesions



Abbreviation: PFS, progression-free survival; BMT, bevacizumab-based maintenance therapy; PD, progressive disease; PFI, platinum-free interval; HGSC, high-grade serous carcinoma

Figure 2. CSS in (A) all patients and (B) patients except for those who discontinued BMT due to reasons other than PD according to histologic type, PFI, extent of secondary cytoreduction and number of recur lesions



Abbreviation: CSS, cancer-specific survival; BMT, bevacizumab-based maintenance therapy; PD, progressive disease; PFI, platinum-free interval; HGSC, high-grade serous carcinoma