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Original Article

Chemotherapy response score no longer predicts survival outcomes in high-grade serous ovarian cancer patients with *BRCA* mutation and/or maintenance therapy

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ABSTRACT

Objective: We aimed to revalidate the chemotherapy response score (CRS) system as a prognostic factor for ovarian cancer patients with breast cancer gene (*BRCA*) mutations or those receiving frontline poly-ADP ribose polymerase (PARP) inhibitors or bevacizumab as maintenance therapy.
Methods: A retrospective analysis was performed using medical records of patients with high-grade serous carcinoma who received neoadjuvant chemotherapy followed by interval debulking surgery between January 2007 and December 2021 at 5 tertiary medical institutions in South Korea. At each hospital, pathologists independently assessed each slide of omental tissues obtained from surgery using the CRS system. Progression-free survival (PFS) and overall survival (OS) values were obtained using Kaplan-Meier analysis to evaluate the effect of *BRCA* mutation, maintenance therapy, and CRS on survival time.
Results: Of 466 patients, *BRCA* mutations were detected in 156 (33.5%) and 131 (28.1%) were treated with maintenance therapy; 98 (21.0%) and 42 (9.0%) were treated with PARP inhibitors or bevacizumab, respectively. Patients with CRS3 had significantly longer PFS than those with CRS1 or 2 (24.7 vs. 16.8 months, p<0.001). However, there was no significant difference in PFS improvement between CRS3 patients and those with CRS1 or 2 with *BRCA* mutation (22.0 vs. 19.3 months, p=0.193). Moreover, no significant PFS prolongation was observed in CRS3 patients compared to CRS1 or 2 patients treated with PARP inhibitors or bevacizumab (24.3 vs. 22.4 months, p=0.851; 27.5 vs. 15.7 months, p=0.347, respectively).
Conclusion: CRS may not be a prognostic factor in patients with *BRCA* mutations and those receiving frontline maintenance therapy.

Keywords: Ovarian Cancer; Neoadjuvant Chemotherapy; *BRCA1* Protein; *BRCA2* Protein; PARP Inhibitors; Bevacizumab

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Synopsis
Our multi-center cohort study revealed that chemotherapy response score may not reflect the survival outcomes in high-grade serous carcinoma patients with the breast cancer gene (*BRCA*) mutations or those receiving maintenance therapy. Pathologic complete response is an eligible prognostic factor for patients with *BRCA* mutations.

INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy in developed countries. Even though the incidence and mortality rates of ovarian cancer, particularly the serous and endometrioid types [1], have decreased over the past decade, it remains the fifth leading cause of cancer-related death in the United States [2-4].

Primary debulking surgery followed by platinum and taxane-based adjuvant chemotherapy remains the standard treatment for advanced-stage epithelial ovarian cancer. However, several randomized clinical trials (CHORUS, ENGOT, SCORPION) have shown that neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) is not inferior to primary debulking surgery in terms of survival outcomes, morbidity, and mortality. Recently, NAC followed by IDS has become an alternative treatment for patients with specific contraindications preventing surgery or those with unresectable disease [5-9]. Despite the increasing number of patients undergoing NAC before debulking surgery, there is no consistent consensus regarding the histopathological response to NAC for high-grade serous carcinoma (HGSC). Böhm et al. [10] proposed a 3-tiered histopathological grading system for assessing NAC response in advanced HGSC, called the chemotherapy response score (CRS). The CRS system stratifies patients into 3 groups, CRS1, 2, and 3, according to the degree of omental or adnexal tissue response to chemotherapy visible on examination. Several subsequent studies have reported a significant association between CRS and progression-free survival (PFS). According to research, CRS3 is independently correlated with a better survival outcome and can be used as a surrogate marker in HGSC [11-13].

Similarly, breast cancer gene (*BRCA*) mutations, known as the most commonly mutated genes in epithelial ovarian cancer patients [14], have been recognized as predictors of chemosensitivity and a prognostic factor for overall survival (OS). It was revealed that *BRCA1* or *2* mutations were associated with a better clinical response rate to platinum-based chemotherapy and improved survival [15]. Few studies [16,17] have analyzed the impact of BRCA mutational status on survival outcomes according to CRS. Contrary to the patients with *BRCA* wild-type, it was revealed that CRS3 did not improve PFS in patients with *BRCA* mutation compared to CRS1 or 2 [16,17]. These results signify that the CRS system may not be a prognostic factor in particular cases including gene alternations, microenvironmental change of tumor, or additional treatment.

Recently, ovarian cancer treatment has been enriched with numerous emerging target therapies, especially antiangiogenic drugs and poly-ADP ribose polymerase (PARP) inhibitors, which have altered the natural course of the disease [1,18]. Moreover, since bevacizumab and PARP inhibitors were approved as maintenance therapy for newly diagnosed epithelial ovarian cancer, predicting prognosis has become more complicated.

Nevertheless, no studies have been conducted to verify the efficacy of the CRS system as a prognostic factor during the maintenance therapy era.

This study aimed to revalidate the CRS system as a surrogate marker in patients with *BRCA* mutations or those receiving the first-line maintenance therapy. In this study, we analyzed the relationship between the CRS system and survival outcomes accounting for *BRCA* mutation status or frontline maintenance therapy including PARP inhibitors and bevacizumab.

MATERIALS AND METHODS

1. Study populations

We retrospectively analyzed the electronic medical records of patients with high-grade serous ovarian, fallopian tube, or peritoneal cancer who underwent NAC followed by IDS between January 2007 and December 2021 at 5 tertiary medical institutions in South Korea. Eligible patients included women who underwent 3 cycles of NAC after histologically confirmed HGSC and reported omental CRS results. As the CRS system is based on omental assessment [10], we excluded patients with only an adnexal CRS result. Institutional Review Board (IRB) approval from Yonsei University College of Medicine was obtained (IRB No. 4-2022-0540). Given that the study used retrospectively collected data, the requirement for written informed consent was waived by the IRB.

All patients enrolled in the study underwent diagnostic imaging assessments, including computed tomography (CT), magnetic resonance image, and positron emission tomography/CT. Additionally, pathologic confirmation was conducted using tissue or ascites obtained before initiating NAC, and all patients were tested for germ-line *BRCA1/2* genes. The criteria for selecting NAC followed by IDS were based on the following factors: 1) the presence of pulmonary and/or hepatic parenchymal metastasis on imaging findings; 2) a high tumor volume that would make optimal debulking surgery impractical, such as a Fagotti's score over 8 or severe mesenteric seeding metastasis; or 3) the medically inoperable status of patients. After 3 cycles of NAC, all patients underwent IDS, which included hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and paraaortic lymphadenectomy. These procedures were performed by experienced gynecological oncologists at each institution, with or without additional radical surgeries. The CRS was determined by expert pathologists at each institution using omental tissue obtained during the IDS. Subsequently, patients received 3–6 cycles of postoperative adjuvant chemotherapy after IDS, adhering to platinum-based chemotherapy in accordance with National Comprehensive Cancer Network guidelines [19] for both NAC and POAC. After completing the standard first-line treatment, specific patients received maintenance therapy. The choice of maintenance therapy was determined by experienced gynecologic oncologists at each hospital following the maintenance therapy guidelines [19,20]. PARP inhibitors, including olaparib, niraparib, or rucaparib, were selected based on the presence of *BRCA* mutations or homologous recombination deficiency (HRD) status. Bevacizumab was administered at a dosage of 15 mg/kg every 3 weeks.

Calculations of sample size were based on a previous study [16,17], which presented the ratio of CRS3 and hazard ratio (HR) as approximately 0.3 and 0.7, respectively. With a 2-sided type I error rate of 5%, a power of 80%, and the use of a log-rank test, we estimated that we would need to examine 377 patients for this study.

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2. Pathologic review

The resected specimens from IDS were formalin-fixed and paraffin-embedded according to standard procedures. All slides stained with hematoxylin and eosin were reviewed in each medical institution's department of pathology. The slide with the most viable tumor and/or the least response to chemotherapy was selected. Since the 3-tier CRS system applied to omental samples is highly reproducible and easily applied by pathologists [10,21,22], 3 pathologists at each hospital independently assessed each slide based on the CRS system proposed by Böhm et al. [10]. The 3-tier CRS system is defined as follows: CRS1: minimal or no tumor response, CRS2: readily identifiable tumor response with viable tumor remaining, and CRS3: complete or near-complete response with no residual tumor. Based on a previous study [10], patients with CRS1 and CRS2 were classified into a single group. We also identified patients with pathologic complete response (pCR), defined as the absence of residual invasive cancer on histologic evaluation of all surgical specimens following completion of NAC [23].

3. Statistical analysis

Descriptive data were reported as medians (range) or frequencies (percentage). Categorical variables were compared using χ^2 test, while continuous variables were analyzed using Student's t-test or Mann-Whitney U test for parametric and non-parametric variables. The Kaplan-Meier analysis was conducted using the log-rank test to estimate survival outcomes and create PFS and OS curves. PFS represented time from diagnosis to first disease recurrence or death for any cause, while OS measured time from diagnosis to death or censored at the date of the last follow-up. Univariate and multivariate Cox regression hazard models calculated adjusted HRs with 95% confidence intervals (CIs) for PFS and OS. Statistical significance was defined as $p<0.05$. SPSS Statistics 26 software (SPSS Inc., Chicago, IL, USA) performed all statistical analyses.

RESULTS

In our study cohort, a total of 466 patients were included; 38, 296, and 132 patients had omental CRSs of 1, 2, and 3, respectively. The general characteristics of patients within each CRS group are described in **Table 1**. The median age of the overall population at diagnosis was 60 years (range 52–67), and the median cancer antigen 125 (CA125) level was 1,277.4 (range 498.8–2,934.8). Additionally, 288 (61.8%) patients exhibited *BRCA* wild-type, while 156 (33.5%) patients had *BRCA1 or 2* mutations. PARP inhibitors were administered to 98 (21.0%) patients, while bevacizumab was given to 42 (9.0%) patients as their first-line maintenance therapy.

Subsequently, a total of 334 (71.7%) patients with an omental CRS of 1 or 2 were grouped together and compared to another group of 132 (28.3%) patients with a CRS3. Of the CRS1 or 2 patients, 210 (62.9%) were without *BRCA1 or 2* mutations, while 108 (32.3%) were affected, and among the CRS3 patients, 78 (59.1%) did not have the mutations, while 48 (36.4%) did ($p=0.942$). After standard chemotherapy, 72 (21.6%) and 26 (19.7%) patients in the CRS1 or 2 and CRS3 groups, respectively, were treated with PARP inhibitors as maintenance therapy ($p=0.658$). The numbers of patients treated with bevacizumab as a frontline maintenance therapy were 30 (9.0%) and 12 (9.1%) in the CRS1/2 and CRS3 groups, respectively ($p=0.944$). Sixteen patients (3.4%) achieved pCR. There were no statistically significant differences between the CRS1/2 and the CRS3 groups with respect to median age, CA125 level, the International Federation of Gynecology and Obstetrics (FIGO) stage, *BRCA* status, and maintenance therapy administered.

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Table 1. Patients and clinical characteristics

Characteristics	Total (n=466)	CRS1/2 (n=334)	CRS3 (n=132)	p-value
Age (yr)	60 (52–67)	60 (53–67)	59 (51–67)	0.502
CA125 level (U/mL)	1,277.4 (498.8–2,934.8)	1,284.3 (490.5–2,943.1)	1,233.6 (516.5–2,938.3)	0.387
FIGO stage				0.986
III	198 (42.5)	142 (42.5)	56 (42.4)	
IV	268 (57.5)	192 (57.5)	76 (57.6)	
BRCA status				0.942
BRCA wild-type	288 (61.8)	210 (62.9)	78 (59.1)	
BRCA1/2 mutation	156 (33.5)	108 (32.3)	48 (36.4)	
Unknown	22 (4.7)	16 (4.8)	6 (4.5)	
PARP inhibitors				0.658
No	368 (79.0)	262 (78.4)	106 (80.3)	
Yes	98 (21.0)	72 (21.6)	26 (19.7)	
Bevacizumab				0.944
No	417 (89.5)	300 (89.8)	117 (88.6)	
Yes	42 (9.0)	30 (9.0)	12 (9.1)	
Unknown	7 (1.5)	4 (1.2)	3 (2.3)	
Residual disease				<0.001
R0	278 (59.6)	182 (54.5)	96 (72.7)	
Residual ≤1 cm	169 (36.3)	136 (40.7)	33 (25.0)	
Residual >1 cm	14 (3.0)	12 (3.6)	2 (1.5)	
Not available	5 (1.1)	4 (1.2)	1 (0.8)	
pCR				<0.001
No	450 (96.6)	334 (100.0)	116 (87.9)	
Yes	16 (3.4)	0 (0.0)	16 (12.1)	

Values are presented as median (range) or number (%).
BRCA, breast cancer gene; CRS, chemotherapy response score; CA125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly-ADP ribose polymerase; pCR, pathologic complete response.

Kaplan-Meier curves for PFS and OS, stratified by CRS or pCR for overall population are shown in **Fig. 1**. At the final analysis, 299 (64.2%) patients had experienced a recurrence, including 230 (68.9%) and 69 (52.3%) patients in the CRS1/2 and CRS3 groups, respectively. The median PFS of all patients was 19.0 months (95% CI=17.6–20.4). Patients within the CRS3 group showed significantly prolonged PFS compared with patients in the CRS1/2 group (24.7 vs. 16.8 months, p<0.001). At the time of analysis, 365 (78.3%) patients were still alive, while 72 (21.6%) and 29 (22.0%) patients with CRS1/2 and CRS3, respectively, had died. There was no statistically significant improvement in OS, but patients with CRS3 showed a trend toward better survival outcomes. The median OS of all patients was 85.5 months (95% CI=74.8–96.3), while that of patients within the CRS1/2 and CRS3 groups was 79.2 months (95% CI=61.6–96.7) and 86.2 months (95% CI=80.6–91.8), respectively (p=0.085). Contrary to the CRS, there were statistically significant survival improvements in patients who achieved pCR for both PFS and OS (p<0.001, p=0.038, respectively). Only 2 (12.5%) patients with pCR experienced recurrence, and all patients with pCR were alive.

Next, we conducted a subgroup analysis for PFS to evaluate the relationship between the CRS group and the subgroups: *BRCA* mutation and frontline maintenance therapy, such as PARP inhibitors and bevacizumab. Kaplan-Meier curves for PFS stratified by CRS according to subgroups are shown in **Fig. 2**. As with the overall population, CRS3 in patients without the *BRCA* mutation showed significant association with improved PFS (p<0.001). However, there was no significant PFS improvement in the CRS3 group compared to that in the CRS1/2 group in patients with the *BRCA* mutation (p=0.193). In the CRS1/2 and CRS3 groups, 66 (61.1%) and 26 (54.2%) patients, respectively, had experienced recurrence at the time of analysis, and the median PFS of patients in the CRS1 or 2 and CRS3 groups with the *BRCA* mutation was 19.3 (95% CI=16.1–22.4) and 22.0 (95% CI=16.8–27.2) months, respectively. CRS3 was

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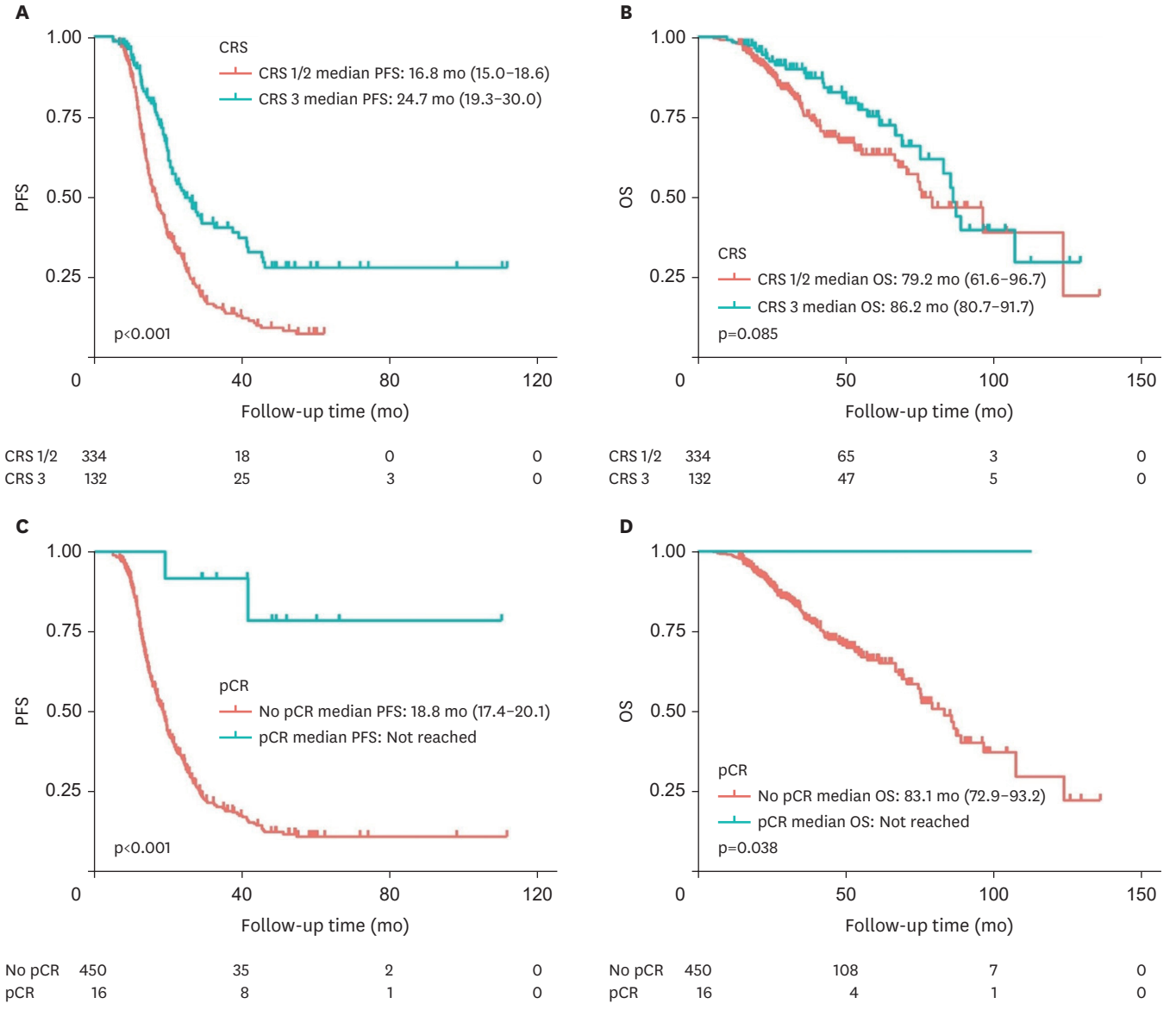

Fig. 1. Kaplan-Meier curves of (A) PFS, (B) OS according to CRS, and (C) PFS, (D) OS stratified by pCR for the overall population.
CRS, chemotherapy response score; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival.

not associated with PFS prolongation in patients receiving frontline maintenance therapy, whereas patients in the CRS3 group who had not undergone frontline maintenance therapy had significantly improved PFS compared to those in the CRS1/2 group. Specifically, the median PFS of patients in the CRS1 or 2 and CRS3 groups undergoing PARP-inhibitor treatment was 22.4 (95% CI=17.8–27.0) and 24.3 (95% CI=14.5–34.2) months, respectively (p=0.851). The median PFS of the CRS1/2 and CRS3 in patients with bevacizumab administration was 15.7 (95% CI=10.5–21.0) and 27.5 (95% CI=6.60–48.4) months, respectively, and no statistically significant difference was observed (p=0.347). Contrary to the overall population, univariate analysis for PFS showed that CRS3 is not a prognostic factor in patients with the *BRCA* mutation (HR=0.74; 95% CI=0.47–1.17; p=0.195) or who are treated with PARP inhibitors (HR=0.93; 95% CI=0.42–2.04; p=0.851) or bevacizumab (HR=0.65; 95% CI=0.26–1.62; p=0.351) (**Fig. 2**). The proportional distribution of PARP inhibitors or bevacizumab based on the presence of the

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BRCA mutation is depicted in **Table S1**. Furthermore, an additional univariate Cox analysis was conducted to evaluate the PFS in relation to the BRCA mutation and the administration of PARP inhibitors. The observed statistically significant differences were confined to BRCA wild-type patients who did not receive PARP inhibitors, specifically between CRS3 and CRS1 or 2 (HR=0.36; 95% CI=0.25–0.53; p<0.001) (**Fig. S1**).

We conducted additional subgroup analyses to determine whether the effect of the *BRCA* mutation on PFS differed by pCR (**Fig. 3**). As with CRS, patients with wild-type *BRCA* with pCR exhibited better PFS than those without pCR (p<0.001). Moreover, in patients with the *BRCA* mutation, pCR was associated with improving PFS, even though it was not statistically

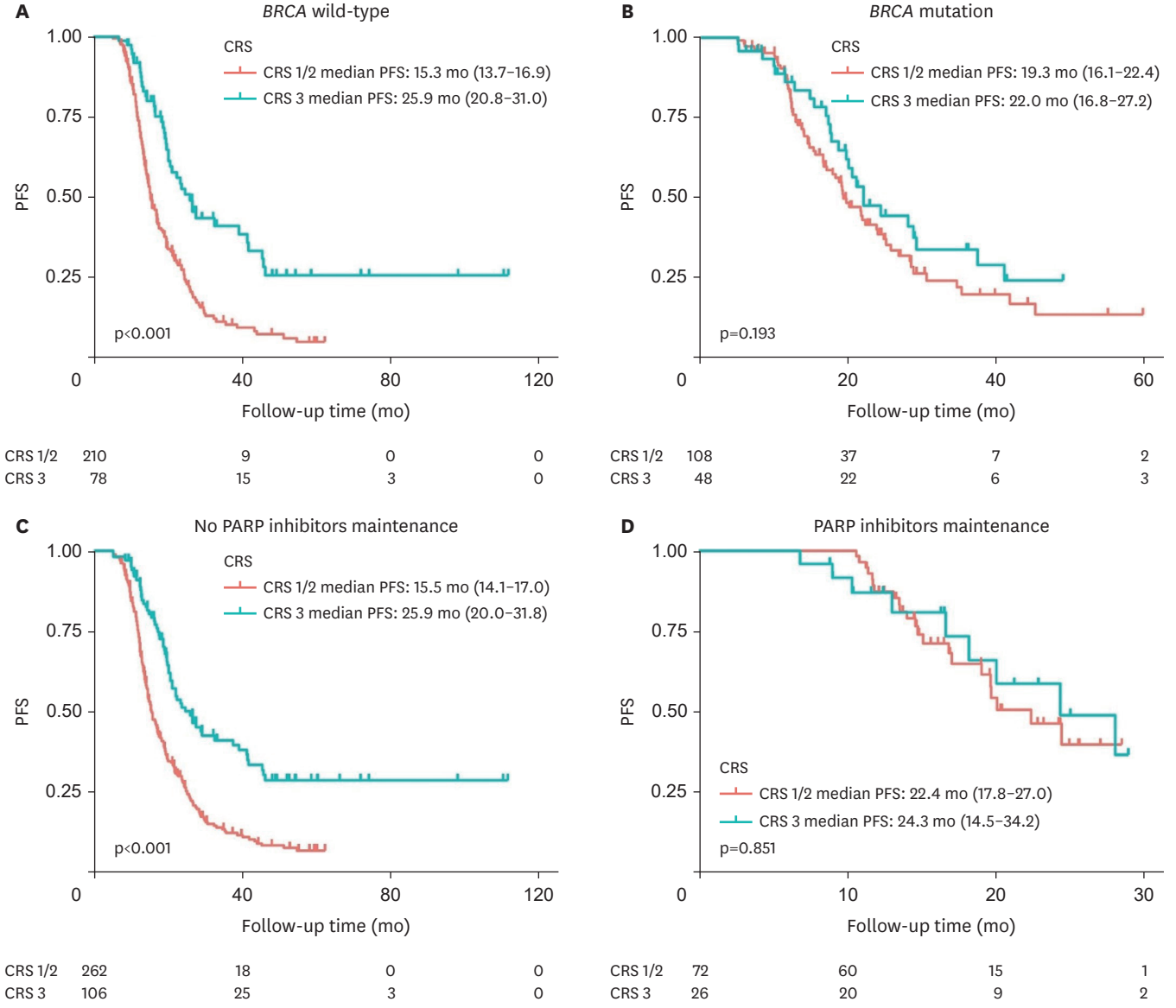

Fig. 2. Kaplan-Meier curves of PFS stratified by CRS according to subgroups. (A) *BRCA* wild-type population. (B) *BRCA* mutation population. (C) No PARP inhibitors maintenance. (D) PARP inhibiters maintenance. (E) No bevacizumab maintenance. (F) Bevacizumab maintenance. (G) Forest plot of HRs of PFS according to baseline clinical subgroups.
BRCA, breast cancer gene; CI, confidence interval; CRS, chemotherapy response score; HR, hazard ratio; PARP, poly-ADP ribose polymerase; PFS, progression-free survival.
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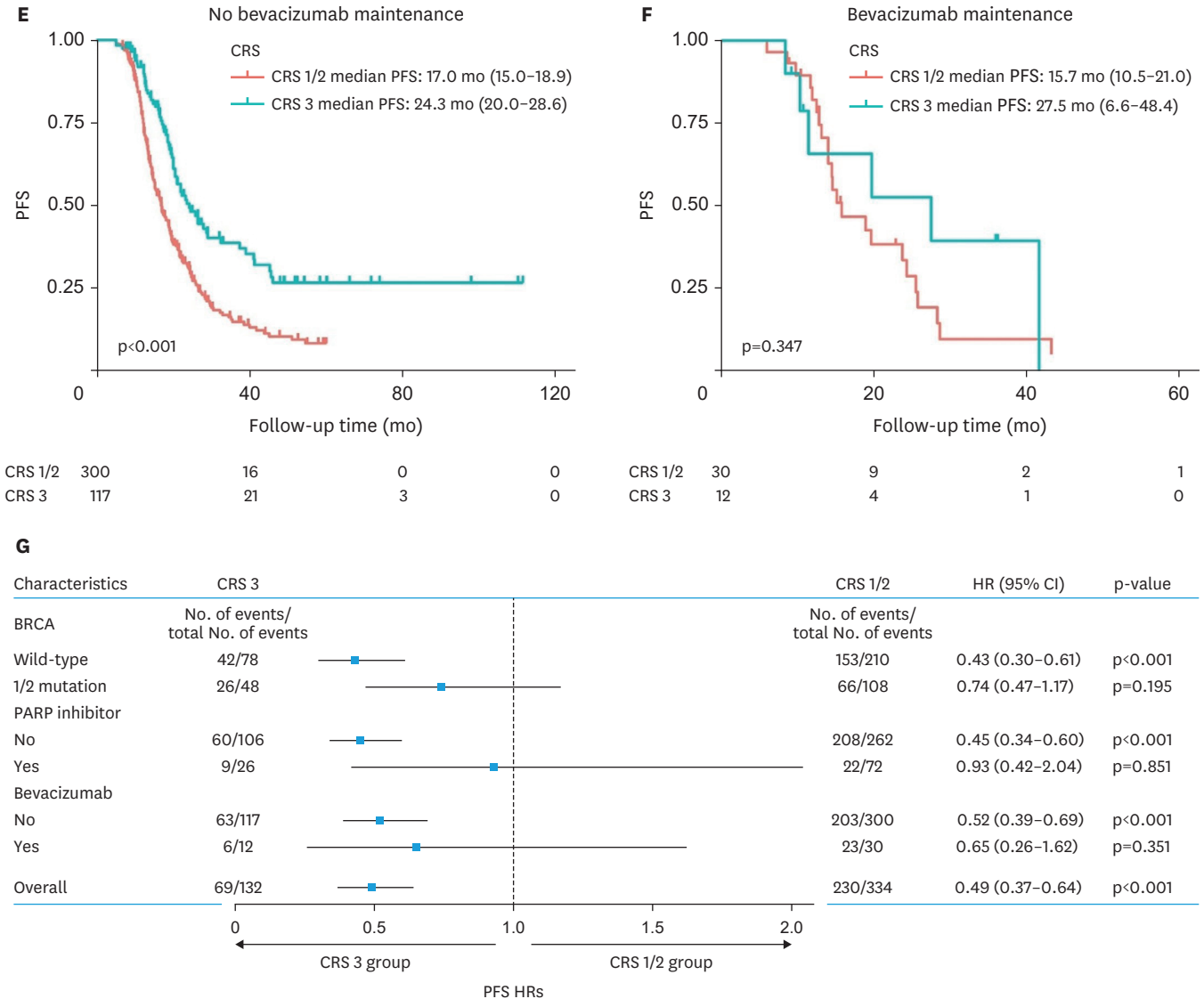

Fig. 2. (Continued) Kaplan-Meier curves of PFS stratified by CRS according to subgroups. (A) *BRCA* wild-type population. (B) *BRCA* mutation population. (C) No PARP inhibitors maintenance. (D) PARP inhibiters maintenance. (E) No bevacizumab maintenance. (F) Bevacizumab maintenance. (G) Forest plot of HRs of PFS according to baseline clinical subgroups.
BRCA, breast cancer gene; CI, confidence interval; CRS, chemotherapy response score; HR, hazard ratio; PARP, poly-ADP ribose polymerase; PFS, progression-free survival.

significant (p=0.054). Only 4 (2.6%) patients with the *BRCA* mutation achieved pCR, and none experienced recurrence. The clinical characteristics of patients, stratified by pCR, are presented in **Table 2**. There were no statistically significant differences observed between the patients who achieved pCR and those who did not achieve pCR in terms of age, CA125 levels, FIGO stage, BRCA status, and administration of bevacizumab.

Univariate and multivariate Cox proportional hazard models for PFS and OS are shown in **Table S2**. The independent prognostic factors for PFS were CRS (HR=0.52; 95% CI=0.40–0.69; p<0.001) and treatment with PARP inhibitors (HR=0.62; 95% CI=0.42–0.91; p=0.013). *BRCA* mutation status (HR=0.42; 95% CI=0.25–0.68; p<0.001) was the only independent prognostic factor for OS.

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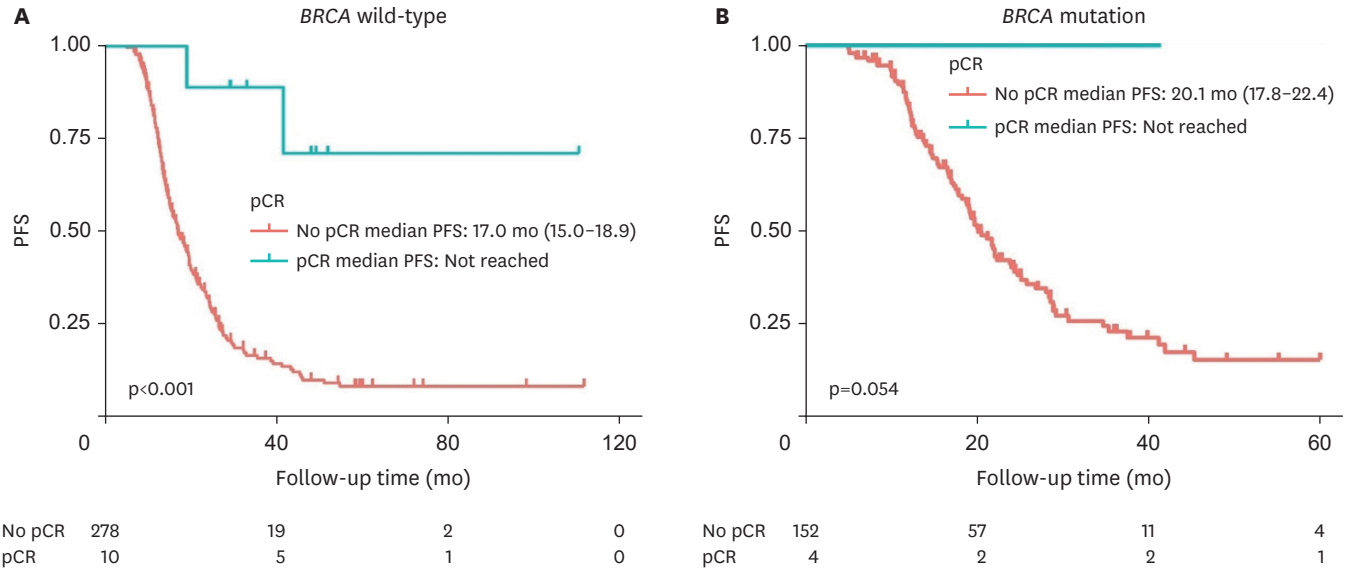

Fig. 3. Kaplan-Meier curves of PFS stratified by pCR according to (A) *BRCA* wild-type and (B) *BRCA* mutation groups.
BRCA, Breast cancer gene; pCR, pathologic complete response; PFS, progression-free survival.

Table 2. Patients and clinical characteristics stratified by pCR

Characteristics	No pCR (n=450)	pCR (n=16)	p-value
Age (yr)	59 (52–67)	62 (52–73)	0.233
CA125 level (U/mL)	1,277.4 (505.5–2,934.8)	1,148.7 (139.2–2,804.9)	0.309
FIGO stage			0.257
III	189 (42.0)	9 (56.3)	
IV	261 (58.0)	7 (43.8)	
BRCA status			0.307
BRCA wild-type	278 (61.8)	10 (62.5)	
BRCA1/2 mutation	152 (33.8)	4 (25.0)	
Unknown	20 (4.4)	2 (12.5)	
PARP inhibitors			0.030
No	352 (78.2)	16 (100.0)	
Yes	98 (21.8)	0 (0.0)	
Bevacizumab			0.257
No	403 (89.6)	14 (87.5)	
Yes	41 (9.1)	1 (6.3)	
Unknown	6 (1.3)	1 (6.3)	

Values are presented as median (range) or number (%).
BRCA, breast cancer gene; CA125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly-ADP ribose polymerase; pCR, pathologic complete response.

DISCUSSION

This study reaffirms that patients who achieved CRS3 represented significantly improved survival outcomes compared to those with CRS1 or 2. The results demonstrate consistency with prior research on CRS, providing further evidence supporting the role of CRS as a prognostic factor. However, unlike the overall population, survival outcomes in patients with the *BRCA* mutation or those receiving maintenance therapy were not stratified by CRS. CRS3 in patients with *BRCA* wild-type or those receiving standard chemotherapy only showed favorable survival outcomes as in the overall population. Our data suggest that the 3-tier omental CRS system does not reflect the survival outcomes in advanced-stage ovarian cancer patients with the *BRCA* mutation or those receiving frontline maintenance therapy, including

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PARP inhibitors or bevacizumab. Unlike the CRS system, pCR may be related to superior survival outcomes in patients with and without *BRCA* mutations.

Occasional studies have reported, but without a definitive explanation, that the CRS system may not be a prognostic factor in patients with the *BRCA* mutation. One possible explanation is that the CRS system, limited to the omental score, does not properly reflect the degree of disease in patients with the *BRCA* mutation associated with wider peritoneal spread and bulky lymph nodes [16,17]. Moreover, in contrast to previous studies [10,12], Santoro et al. [24] revealed that the adnexal CRS system is both reproducible and prognostic, similar to the omental CRS system. Therefore, if the omental CRS system is not feasible, it is suggested to consider the adnexal CRS system as a potential prognostic factor. In addition, the adnexal CRS system is more suited to reflect the platinum resistance than the omental CRS system [12,25]. Therefore, the omental CRS system is insufficient as a prognostic factor in patients with *BRCA* mutations. Subsequent research may be needed to investigate the prognostic effect of the adnexal CRS system in patients with BRCA mutations and/or in those who have undergone maintenance therapy with PARP inhibitors or bevacizumab.

Ergasti et al. [17] reported that patients with the *BRCA* mutation achieved a higher proportion of CRS3 than those with *BRCA* wild-type. However, there was no significant difference in the proportion of CRS3 according to the *BRCA* mutation. Because we only enrolled patients who received 3 times of NAC, the resulting ratio differed from that in previous studies [17] involving patients who underwent 3 or 4 times of NAC. Nevertheless, we confirmed that the CRS system was not a reliable prognostic factor in patients with the *BRCA* mutation.

No study has investigated whether the CRS system is still effective as a prognostic factor in the maintenance therapy era. Lodewijk et al. [26] analyzed the modification of immune-related gene expression profiles by NAC in epithelial ovarian cancer. They confirmed significant beneficial immune profile changes, such as immune-cell adhesion and migration and lymphoid and myeloid compartment remodeling in only CRS1/2 patients after paclitaxel or carboplatin-based NAC. Even in the CRS3 group, significant stimulation of transforming growth factor-beta signaling was found after NAC. Based on this result, they considered that the patients who responded poorly to NAC could be effective candidates for immunotherapy. Furthermore, it is known that addition of PARP inhibitors may improve its immunogenicity by increasing cell death and, consequently, cytosolic DNA production [27]. This was consistent with our clinical results, which demonstrated no difference between the CRS in patients receiving maintenance therapy.

This is the first study to report that the CRS system may not reflect survival outcomes in patients treated with frontline maintenance therapy. Moreover, this is the largest multi-center study to date to revalidate the correlation between the CRS system and survival outcomes in patients with the *BRCA* mutation. In this study, we re-verified the association between the CRS system and survival outcomes and evaluated the impact of *BRCA* mutation on the CRS system.

The main limitations of this study were the retrospective nature of data collection and small sample size in some subgroups. Although the study included more than the required number of patients, some subgroups, such as the bevacizumab-treated group, were assigned only a small number of patients. Moreover, given the prolonged duration of data collection, it is challenging to completely exclude the possibility of time bias. However, considering the

majority (over 95%) of patients were diagnosed with ovarian cancer after 2014, the potential impact of time bias resulting from differences in treatment is expected to be minimal. Second, we only analyzed the patients with germline *BRCA* mutation. As we revealed that the germline *BRCA* mutation and PARP inhibitors may affect prognosis, further studies are required to evaluate patients with the somatic *BRCA* mutation or HRD.

In conclusion, the CRS system may not be a surrogate marker in patients with the *BRCA* mutation or those receiving frontline maintenance therapy. The pCR may be a reliable prognostic factor regardless of *BRCA* mutations. Nonetheless, it is necessary to contrive a new surrogate model to predict survival outcomes in the maintenance era.

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SUPPLEMENTARY MATERIALS

Table S1

BRCA mutation status relative to maintenance therapy

Table S2

Cox proportional hazard models of prognostic factors for recurrence and death adjusted for CRS, *BRCA* status, maintenance therapy, and residual disease status

Fig. S1

Forest plot of HRs for PFS according to the *BRCA* mutation and PARP inhibitors.

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