

Original Article



Prognostic value of complete metabolic response on ¹⁸F-FDG-PET/CT after three cycles of neoadjuvant chemotherapy in advanced high-grade serous ovarian cancer

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OPEN ACCESS

Received: Aug 23, 2021

Revised: Dec 6, 2021

Accepted: Dec 26, 2021

Published online: Jan 17, 2022

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ABSTRACT


Objective: We investigated the prognostic value of complete metabolic response (CMR) on ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) after 3 cycles of neoadjuvant chemotherapy (NAC) in advanced high-grade serous ovarian cancer (HGSC).

Methods: PET/CT at baseline and after 3 cycles of NAC were performed; peak standardized uptakes were measured. PET parameters were compared with NAC parameter: cancer antigen-125 (CA-125) normalization before interval debulking surgery (IDS) and chemotherapy response score (CRS) to predict platinum-sensitivity. Kaplan-Meier analysis was used to determine correlations between PET parameters and survival. Prognostic factors were obtained by multivariate Cox regression analysis.

Results: Between 2007 and 2020, 102 patients were recruited: 19 (18.6%) were designated as CMR group and 83 (81.4%) as non-CMR group. CMR after 3 cycles of NAC showed the highest accuracy in predicting platinum-sensitivity (area under the curve [AUC]=0.729; 95% confidence interval [CI]=0.552–0.823; p=0.017), compared with CA-125 normalization before IDS (AUC=0.626; 95% CI=0.542–0.758; p=0.010) and CRS (AUC=0.613; 95% CI=0.490–0.735; p=0.080). CMR demonstrated better prognosis than non-CMR in progression-free survival (PFS) (median PFS, 23.9 months vs. 16.4 months; p=0.021) and overall survival (OS) (median OS, not reached vs. 69.7 months; p=0.025). In multivariate analysis, CMR was associated with a lower risk of recurrence (adjusted hazard ratio [aHR]=0.50; 95% CI=0.27–0.92; p=0.027) and death (aHR=0.23; 95% CI=0.05–0.99; p=0.048).

Conclusion: CMR after 3 cycles of NAC can be a prognostic factor for both recurrence and death in advanced HGSC.

Keywords: Ovarian Neoplasms; Neoadjuvant Therapy; Positron Emission Tomography Computed Tomography; Prognosis

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Funding

This research was supported by Shin Poong Pharm. Co. Ltd.

Conflict of Interest

No potential conflict of interest relevant to this article was reported

Author Contributions

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 C.Y.S., K.H.S., K.S.; Funding acquisition:
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 & editing: C.Y.S., K.Y., K.H.S., L.J.Y., K.W.J., K.S.,
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Synopsis

- CMR after NAC can be used to determine the extent of surgery.
- CMR after NAC provides higher accuracy for predicting platinum-sensitivity, compared with cancer antigen-125 normalization before IDS.
- CMR after NAC can be useful for stratifying prognosis in advanced HGSC.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) has become an alternative approach in the treatment of advanced-stage ovarian cancer [1,2]. Tumor response to NAC is strongly associated with survival outcomes. Therefore, it is prudent to distinguish NAC responders from non-responders and identify prognostic factors to improve survival.

Because studies of treatment response evaluation have mainly been conducted in primary debulking surgery settings [3], the number of studies focused on evaluation of NAC response is limited [4]. There is also no suitable method to predict the prognosis of ovarian cancer patients who received NAC before surgery. Currently, computed tomography (CT) is the imaging modality of choice and commonly performed in treatment response evaluation [5]. However, because Response Evaluation Criteria In Solid Tumors (RECIST) is based only on anatomical changes in tumor size, its association between morphological changes and patient outcomes is not clear, especially in the era of novel combination chemotherapy and biological agents [5,6]. One study suggested that CT imaging may not be sufficient to evaluate the NAC response [7].

Positron emission tomography/computed tomography (PET/CT) with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) is a well-established functional imaging modality of choice and is used for the diagnosis and staging of ovarian cancer [8,9]. ¹⁸F-FDG-PET/CT can distinguish viable tumor cells from tumor-independent changes based on the glucose metabolism of tumor tissue [10]. Several studies [11,12], our previous study inclusive [13], have shown that changes of the metabolic activity during NAC can be an indicator in predicting NAC response in ovarian cancer.

Complete metabolic response (CMR), defined as negative findings on the PET scan after neoadjuvant treatment, has been shown to predict survival in some cancers: breast cancer [14] and rectal cancer [15]. In ovarian cancer, however, it is little known whether CMR provides survival benefits or merely indicates a temporary arrest in FDG-uptake with limited clinical impact [16]. To evaluate the prognostic significance of CMR after NAC, we studied the association between FDG-uptake and survival outcome in patients with advanced high-grade serous ovarian cancer (HGSC).

MATERIALS AND METHODS

1. Patients

From 2007 to 2020, medical records of all patients with ovarian cancer in the Severance Hospital at Yonsei University College of Medicine were retrospectively analyzed. The inclusion criteria were as follows: (1) histopathologically confirmed clinical stage III or IV HGSC; (2) received 3 or 4 cycles of NAC; and 3) performed a baseline ¹⁸F-FDG-PET/CT scan before starting NAC and a second scan after 3 cycles of NAC. After NAC, patients underwent

IDS followed by postoperative adjuvant chemotherapy (POAC). Chart review was done to determine patient characteristics, International Federation of Gynecology and Obstetrics staging, metabolic response on ^{18}F -FDG-PET/CT, outcomes of NAC, and survival rate. This study was approved by the Institutional Review Board at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, and requirement for written informed consent was waived due to the retrospective nature of the study.

2. Protocol-based treatment

All patients were clinically staged preoperatively using mammography, breast ultrasonography, esophagogastroduodenoscopy, colonoscopy, pelvic magnetic resonance imaging, chest/abdominal/pelvic CT, and ^{18}F -FDG-PET/CT. Histopathological diagnosis of epithelial ovarian cancer was confirmed by cytology of ascites/pleural effusion, aspiration biopsy, and diagnostic laparoscopic/laparotomy biopsy. Patients diagnosed with epithelial ovarian cancer underwent genetic testing for *BRCA1* and *BRCA2* germline mutations.

NAC was performed when one of the following 3 selection criteria of our institution was met: old patient age and poor performance status; high tumor burden described by the Fagotti scoring system [17] during diagnostic laparoscopy (Fagotti score ≥ 8); and distant metastases, such as pulmonary and/or hepatic parenchymal metastases, identified by the baseline imaging modalities, including ^{18}F -FDG-PET/CT.

After NAC, patients underwent IDS comprising hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy as a standard surgery, with or without radical surgery procedures (e.g., bowel resection, liver resection, splenectomy, and diaphragm/peritoneal surface stripping). Based on the standard protocol of our institution, all surgical procedures were performed to obtain complete or optimal debulking surgery with no gross residual disease or <1 cm at least. NAC and POAC consisted of a combination of taxane and platinum.

3. None

All patients fasted for at least 8 h before PET/CT acquisition to maintain blood glucose concentrations below 140 mg/dL. Patients were intravenously injected with 5.5 MBq of ^{18}F -FDG per kg body weight. Approximately 60 minutes after the tracer injection, integrated PET/CT was performed using a dedicated Discovery STE scanner (GE Medical systems, Milwaukee, WI, USA). For integrated PET/CT images, we used the spiral mode of the CT from the base of the skull to the proximal thighs using the following parameters: 120 kVp, 30 mA, 0.8-second rotation time, 3.75-mm helical thickness, 27 mm per rotation (speed), 2.5-mm scan reconstruction, with a reconstruction index of 1.25 mm, 15.7 cm field of view, and a 512 \times 512 matrix. PET scans were acquired from the cerebellum to the proximal thigh, and PET emission data, in a 3D mode, every 3 min per bed position. Attenuation-corrected PET data were reconstructed using an iterative reconstruction algorithm with a 5-mm slice thickness.

All PET/CT images had been interpreted and confirmed with the consensus of 2 nuclear medicine physicians without knowledge of patients' records. Each region with a higher FDG uptake than the background was considered significant. The standardized uptake value (SUV) was investigated in all cases, and the peak SUV (SUV_{peak}) was obtained by using a circular region of interest (ROI) centered on a high-uptake part of the tumor in the transaxial PET images. Imaging analysis was performed using AW Volume Share 5 (GE Healthcare, Milwaukee, WI, USA). We drew a circular ROI around tumor, and automatically tumor

margin layout was drawn with a threshold of 40% of maximum value. The SUV_{peak} was automatically measured in AW Volume Share 5. This SUV_{peak} ROI was calculated as follows: [Decay-corrected Activity (MBq) per Tissue Volume (mL)]/[Injected ¹⁸F-FDG Dose (MBq) per Body Mass (g)].

4. PET parameters

Nine tumor lesions (right/left upper quadrant, sub-hepatic area, mesentery, pelvis, right/left ovary, mediastinum, and supraclavicular fossa) per patient were identified. For semiquantitative analysis of each lesion showing increased FDG uptake, SUV_{peak} was measured. First, SUV_{peak} on the baseline PET/CT scan was calculated. Then every lesion was also measured in a PET/CT scan performed after 3 cycles of NAC, and SUV_{peak} after 3 cycles of NAC was compared with that of the baseline study. If the lesions could not be measurable in PET/CT scan after 3 cycles of NAC, the values of these lesions were considered zero in this semiquantitative analysis because the lesions could not be detectable. Qualitative analysis was determined from side by side visual inspection of PET/CT images at baseline and after 3 cycles of NAC.

Metabolic responses before and after chemotherapy were defined according to PET response criteria in solid tumors (PERCIST) proposed by Wahl et al. [10]. Based on PERCIST, CMR was defined as complete resolution of ¹⁸F-FDG uptake within measurable target lesions at a level less than the mean liver activity and indistinguishable from the surrounding background and no new pattern of FDG-avid lesions typical for cancer. That is, CMR means that a zero of ¹⁸F-FDG uptake or visual disappearance of all of metabolically active tumors on the PET/CT scan after chemotherapy. Conversely, persistence of abnormal FDG uptake (FDG uptake higher than mean liver activity) was considered as not achieving CMR (non-CMR). The patients were divided into 2 groups: CMR and non-CMR.

5. Assessment of response to NAC

To clinically evaluate the chemotherapy response, cancer antigen-125 (CA-125) and CT scan were performed. CA-125 was considered an important factor for assessing the response to treatment [3], and was determined at baseline, after receiving each NAC cycle, and before IDS. Normalization of CA-125 before IDS was used to assess response to NAC. CA-125 level was classified as normal (<35 U/mL) or high (≥35 U/mL), consistent with the definition of CA-125 normalization commonly used in the clinical setting. As another tool for evaluation of clinical response, CT scan before IDS was performed, and response assessments were based on the RECIST criteria version 1.1 [5]. Complete response (CR) was defined as disappearance of all target lesions, and partial response (PR) as decrease of a target lesion by at least 30% on CT scan.

The chemotherapy response score (CRS) system is a previously validated method for assessing the pathologic response to NAC in ovarian cancer [18,19]. To assess the histopathologic response to NAC, an experienced gynecologic pathologist (K.H.S.), blinded to patients' records, reviewed all available hematoxylin and eosin-stained slides obtained from IDS specimens for signs of tumor regression. Specimens were taken from 3 sites: omentum and right and left adnexa. He scored each slide according to the 3-tiered CRS system proposed by Böhm et al. [19]. Pathologic CR is defined as CRS 3, which means CR or almost CR with no residual tumor. CRS 2 shows considerable tumor response among readily identifiable viable tumors. Specimens with no or minimal signs of tumor regression were classified as CRS 1. In this study, only omental CRS was used to evaluate the pathologic response to chemotherapy, because Böhm et al. [19] and Lee et al. [18] showed significant associations of survival outcome with omental rather than adnexal CRS.

6. Statistical analysis

PET parameters were compared with NAC parameters using the χ^2 and Fisher's exact tests. Progression-free survival (PFS) and overall survival (OS) were evaluated by Kaplan-Meier survival analysis and compared using the log-rank test according to PET parameters. Univariate and multivariate analyses using the Cox regression model were performed to assess factors affecting PFS and OS. PFS was defined as the time interval from the first NAC to the first recurrence and it was the primary endpoint of the study. OS was defined as the time interval from the first NAC to death or last follow-up. The platinum-free interval (PFI) was defined as the duration from the end of the postoperative adjuvant platinum-based chemotherapy to the first recurrence. We chose the threshold value of 12 months to qualify platinum-sensitive disease [20]. The receiver operating characteristics (ROC) curve analysis was performed to evaluate the ability of CMR, CA-125 before IDS, and CRS to predict the platinum-sensitivity. The area under the curve was also calculated. All values were 2-sided and p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS, version 25 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

1. Patient characteristics

We found 119 patients receiving NAC for clinical stage III or IV ovarian cancer in our institutional databases, of which 102 patients met the inclusion criteria. Eight patients with non-HGSC subtype and 6 who underwent 5 or 6 cycles of NAC were excluded for homogeneity of the group. Three patients were also excluded because they were considered to have stable disease or progressive disease before IDS, according to their response rate based on RECIST criteria. The baseline characteristics of 102 patients are summarized in **Table 1**. The patients' median age at diagnosis was 57.5 years (range, 37.0–78.0 years) and their median CA-125 at diagnosis was 1,735.6 U/mL (range, 75.2–14,838.2 U/mL). Of the 102 patients included, 72 (70.6%) had the wild-type *BRCA* genotype, and 22 (21.6%) had the *BRCA1* or *BRCA2* mutations.

All patients received PET/CT examinations before starting NAC and after 3 cycles of NAC. After completing NAC, all patients underwent IDS. The CRS 3 rate was 29.4% (n=30) and the no gross residual disease rate after IDS was 52.0% (n=53). Most of patients were considered to have PR (n=99, 97.1%) and 3 patients (2.9%) had CR before IDS according to RECIST criteria.

PET/CT at baseline was performed before initiation of NAC at a median interval of 6 days (range, 1–49 days). The median time interval between the third cycle of NAC and the second (after the third cycle of NAC) PET/CT was 15 days (range 2–36 days). The median follow-up time was 37.9 months (range, 13.8–158.4 months). During this period, 81 patients (79.4%) experienced recurrence and 26 (25.5%) had died. Fifty patients (49.0%) showed a platinum-sensitivity disease (PFI >12 months). The median PFS was 17.2 months (95% confidence interval [CI], 14.1–20.3 months) and the median OS was not yet reached.

2. Association between CMR and NAC response parameters

In 102 patients, 19 (18.6%) were assigned to the CMR group and 83 (81.4%) to the non-CMR. **Fig. 1** presents examples of CMR and non-CMR seen after 3 cycles of NAC.

In **Table 2**, NAC response parameters are compared between the 2 groups. A higher rate of CA-125 normalization before IDS was found in the CMR group (73.7% vs. 43.4%, p=0.017)

Table 1. Baseline characteristics of the patients (n=102)

Characteristics	Value
Age at diagnosis (yr)	57.5 (37.0–78.0)
BMI at diagnosis (kg/m ²)	23.2 (17.6–40.3)
ASA score at diagnosis	
1	11 (10.8)
2	47 (46.1)
3	44 (43.1)
CA-125 level at diagnosis (U/mL)	1,735.6 (75.2–14,838.2)
CA-125 level before IDS (U/mL)	39.9 (5.7–1,296.2)
FIGO stage	
III	33 (32.4)
IV	69 (67.6)
Histological subtype	
HGSC	102 (100)
BRCA1/2 status	
Wild-type	72 (70.6)
Mutation	22 (21.6)
Not available	8 (7.8)
Regimen of NAC	
Taxane+Platinum	85 (83.3)
Taxane+Platinum+Bevacizumab	17 (16.7)
Cycles of NAC	3 (3–4)
Surgery extent	
Standard*	65 (63.7)
Radical†	37 (36.3)
Method of IDS	
Laparotomy	89 (87.3)
Laparoscopy	13 (12.7)
Residual disease after IDS	
NGR	53 (52.0)
≤1 cm	40 (39.2)
>1 cm	4 (3.9)
Not available	5 (4.9)
CRS	
1	3 (2.9)
2	63 (61.8)
3	30 (29.4)
Not available	6 (5.9)

Values are presented as median (range) or number (%).

ASA, American Society of Anesthesiologists; BMI, body mass index; CA-125, cancer antigen-125; CRS, chemotherapy response score; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; NGR, no gross residual disease.

*Standard surgery included hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy; †Radical included any of following: bowel resection, liver resection, splenectomy, cholecystectomy, diaphragm/peritoneal surface stripping, partial gastrectomy, partial cystectomy/ureteroneocystostomy, and distal pancreatectomy.

and a higher rate of radical surgery was achieved in the non-CMR group (25.8% vs. 41.0%, $p=0.040$). However, there were no statistically significant differences in the rate of CRS 3 (38.9% vs. 29.5%, $p=0.573$) and no residual disease after IDS (57.9% vs. 53.8%, $p=0.751$) in both groups. Interestingly, most patients with CMR did not achieve CRS 3 (38.9%) like patients with non-CMR (29.5%).

3. Association between CMR and survival

The Kaplan-Meier curves and the log rank test result showed that there were differences in PFS and OS between patients who achieved CMR and non-CMR after 3 cycles of NAC; the median PFS of patients with CMR and non-CMR was 23.9 (95% CI=16.9–30.8 months) and 16.4 months (95% CI=13.3–19.4 months), respectively ($p=0.021$) (**Fig. 2A**). The median OS

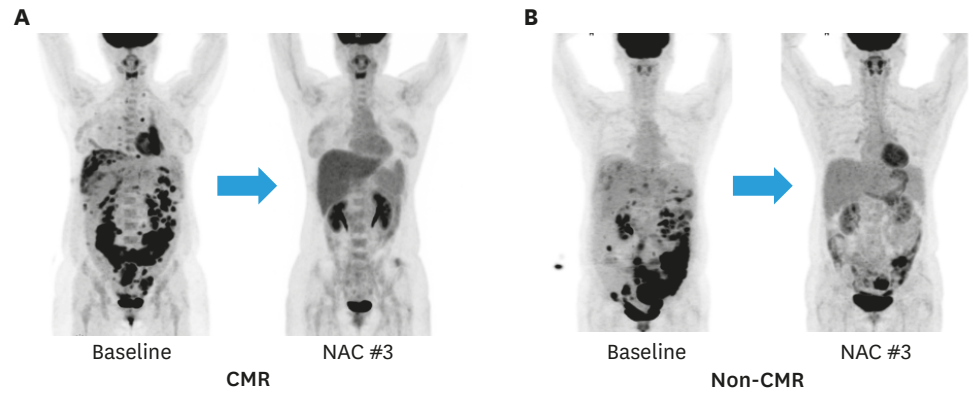


Fig. 1. Representative ¹⁸F-FDG-PET/CT images at baseline and after 3 cycles of NAC in the patient with CMR (A) and non-CMR (B).
 CMR, complete metabolic response; NAC, neoadjuvant chemotherapy; ¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography.

Table 2. Associations between positron emission tomography parameters and outcomes of neoadjuvant chemotherapy (n=102)

Characteristics	CMR group (n=19)	Non-CMR group (n=83)	p-value
Pre-treatment factors			
CA-125 level at diagnosis			0.040
<1,500 U/mL	12 (63.2)	31 (37.3)	
≥1,500 U/mL	7 (36.8)	52 (62.7)	
Post-treatment factors			
CA-125 level before IDS			0.017
<35 U/mL	14 (73.7)	36 (43.4)	
≥35 U/mL	5 (26.3)	47 (56.6)	
Surgery extent			0.040
Standard*	16 (84.2)	49 (59.0)	
Radical†	3 (25.8)	34 (41.0)	
Residual disease after IDS			0.751
NGR	11 (57.9)	42 (53.8)	
>0 cm	8 (42.1)	36 (46.2)	
Not available	1	4	
CRS			0.573
CRS 1/2	11 (61.1)	55 (70.5)	
CRS 3	7 (38.9)	23 (29.5)	
Not available	1	5	

Values are presented as number (%).

CA-125, cancer antigen-125; CMR, complete metabolic response; CRS, chemotherapy response score; IDS, interval debulking surgery; NGR, no gross residual disease.

*Standard surgery included hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy; †Radical included any of following: bowel resection, liver resection, splenectomy, cholecystectomy, diaphragm/peritoneal surface stripping, partial gastrectomy, partial cystectomy/ureteroneocystostomy, and distal pancreatectomy.

was 69.7 months (95% CI=12.9–139.0 months) in the non-CMR group and not yet reached in the CMR group (p=0.025) (**Fig. 2B**).

A subgroup analysis was performed to explore the relationship of CMR to pathologic response. Among CMR patients, there was no significant difference in PFS (p=0.681) or OS (p=0.218) between those with CRS 3 and those with CRS 1/2 (**Fig. S1**). In the non-CMR group, patients with CRS 3 had improved PFS (p=0.033) compared with patients having CRS 1/2, but not in the OS (p=0.586) (**Fig. S2**). In addition, we compared CMR and non-CMR in patients with and without *BRCA1/2* mutation (**Fig. S3** and **S4**). In the *BRCA1/2* wild-type group, patients with CMR tended to have better PFS (p=0.103) and OS (p=0.050) than those in non-CMR

Prognostic role of CMR in ovarian HGSC

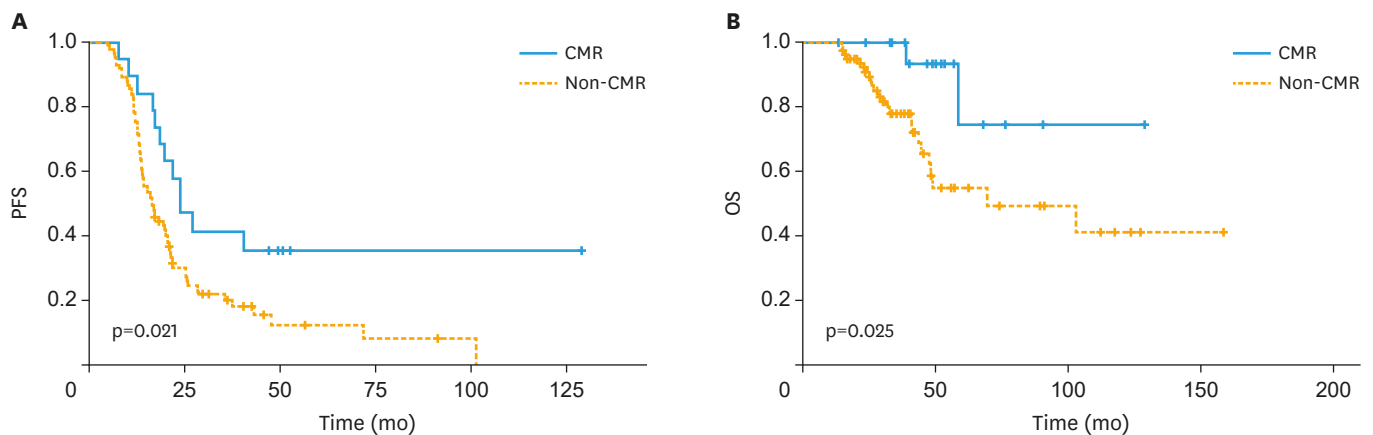


Fig. 2. Kaplan-Meier survival curves of PFS (A) and OS (B) according to achievement of CMR. CMR, complete metabolic response; OS, overall survival; PFS, progression-free survival.

patients (**Fig. S3**). However, in patients with *BRCA1/2* mutation, there was no significant difference in the PFS ($p=0.244$) and OS ($p=0.214$) between both groups (**Fig. S4**).

In **Table 3**, factors associated with both PFS and OS were determined using univariate and multivariate analyses. In multivariate analysis, CMR was identified as an independent prognostic factor for both PFS (adjusted hazard ratio [aHR]=0.498; 95% CI=0.260–0.955; $p=0.027$) and OS (aHR=0.238; 95% CI=0.055–0.985; $p=0.048$). Other possible confounders such as age, CA-125 level before IDS, residual disease after IDS, and surgery extent were not associated with PFS and OS after adjustment for the factors by multivariate Cox proportional hazard model. To assess the ability of CMR, CA-125 normalization before IDS, and CRS to predict the platinum-sensitivity, the ROC curve was carried out (**Fig. 3**). The areas under the ROC curves for the prediction of platinum-sensitivity were 0.729 (95% CI=0.552–0.823; $p=0.017$) for CMR, 0.626 (95% CI=0.542–0.758; $p=0.010$) for CA-125 normalization before IDS, and 0.613 (95% CI=0.490–0.735; $p=0.080$) for CRS (**Table S1**). There was no significant difference in PFS ($p=0.056$) and OS ($p=0.234$) between CRS 3 and CRS 1/2 (**Fig. S5**), while patients with normalized CA-125 before IDS had better PFS ($p=0.001$) and OS ($p=0.004$) than those without (**Fig. S6**).

Table 3. Univariate and multivariate Cox regression analyses of progression-free survival and overall survival

Variables	Progression-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	aHR (95% CI)	p-value	HR (95% CI)	p-value	aHR (95% CI)	p-value
Age	1.008 (0.986–1.030)	0.484	1.013 (0.988–1.038)	0.324	0.999 (0.959–1.039)	0.942	1.004 (0.958–1.053)	0.855
CA-125 before IDS	1.001 (1.000–1.002)	0.023	1.001 (1.000–1.001)	0.194	1.001 (1.000–1.002)	0.106	1.001 (0.999–1.002)	0.254
Residual disease after IDS								
NGR	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
>0 cm	1.119 (0.713–1.758)	0.624	1.101 (0.685–1.769)	0.692	1.050 (0.453–2.432)	0.909	1.065 (0.444–2.554)	0.888
Surgery extent								
Standard*	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
Radical†	1.381 (0.882–2.164)	0.159	1.034 (0.601–1.779)	0.905	1.504 (0.687–3.292)	0.307	1.116 (0.444–2.806)	0.816
CMR								
No	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
Yes	0.489 (0.264–0.908)	0.021	0.498 (0.260–0.955)	0.027	0.219 (0.051–0.935)	0.040	0.238 (0.055–0.985)	0.048

aHR, adjusted hazard ratio; CA-125, cancer antigen-125; CI, confidence interval; CMR, complete metabolic response; HR, hazard ratio; IDS, interval debulking surgery; NGR, no gross residual disease.

*Standard surgery included hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy; †Radical included any of following: bowel resection, liver resection, splenectomy, cholecystectomy, diaphragm/peritoneal surface stripping, partial gastrectomy, partial cystectomy/ureteroneocystostomy, and distal pancreatectomy.

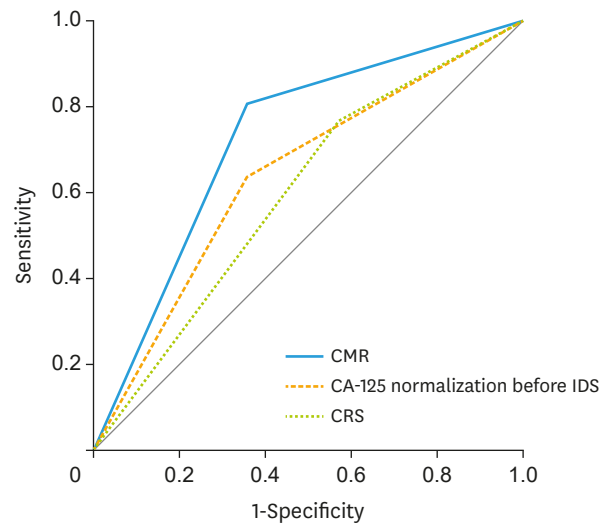


Fig. 3. Receiver operating characteristic analysis of CMR (A), normalization of CA-125 level before IDS (B), CRS (C) for the prediction of platinum-sensitivity. CA-125, cancer antigen-125; CMR, complete metabolic response; CRS, chemotherapy response score; IDS, interval debulking surgery.

DISCUSSION

This study aimed to investigate the clinical role of ¹⁸F-FDG-PET/CT after NAC in ovarian cancer, highlighting the significance of CMR. Consequently, our results suggested that CMR after 3 cycles of NAC can be associated with reduced risk of recurrence and death in advanced HGSC.

There have been several studies on the relationship between CMR on PET/CT and survival after neoadjuvant therapy in various cancers [14-16]. In breast cancer, Chen et al. [14] concluded that CMR after NAC is an independent prognostic factor and indicates a significantly better prognosis. Yeung et al. [15] reported that CMR after neoadjuvant therapy predicts a lower risk of recurrence and death and can help stratify the prognosis in rectal cancer. In ovarian cancer, however, there is currently a lack of information regarding the prognostic value of CMR after NAC. In 2019, Watanabe et al. [16] showed that CMR after NAC in ovarian cancer has prognostic potential, especially in PFS. However, there were some limitations: small number of patients (n=22) were included, second PET/CT scans were performed after various and different NAC cycles (n=2,3,4,6), and assessment of pathological response and multivariate analysis in PFS or OS were not performed. In our study, patients with CMR had a lower risk of recurrence and death, which is consistent with the results of other studies [14-16].

Pathologic CR can be considered a surrogate marker of survival in patients receiving neoadjuvant therapy in various cancers [18,19,21,22]. Therefore, it is important in predicting pathologic CR or prognosis prior to surgery, and sequential PET/CT scans during neoadjuvant therapy were noted to be a surrogate for predicting pathologic CR and for improved survival in many cancers [13,23,24]. These studies judged response based on the reduction rate of SUV, with various predicted cut-offs. From the current literature, it is not clear whether CMR evaluated by PET/CT reflects pathologic CR in different cancers [15,25,26]. One study showed that CMR has a significant correlation with pathologic CR [25]. Other studies reported that CMR did not uniformly predict pathologic CR [15,26]. In our study, CMR was

not substantially predictive of CRS 3, raising the question that higher magnitude of tumor metabolic changes may not reflect the CRS 3 rates.

Our result suggested that most patients with CMR still had viable tumor cells in situ, and this discordance could be due to the reduction or loss of FDG avidity as tumor size decreases. Considering the kinetics of tumor cell killing and its relationship to PET/CT, increasing the number of chemotherapy cycles reduces the number of cancer cells that can be detected by PET/CT [10]. This indicates that a negative PET/CT scan after treatment does not necessarily mean the absence of cancer cells, and that there may be viable tumor cells below the level of detection. On the other hand, a positive PET/CT is only an indicator of active disease. This may cause a significant difference in the recurrence rate between patients with CRS 3 and CRS 1/2 in the non-CMR group, unlike in the CMR group (**Fig. S1** and **S2**). Despite the discordance between metabolic and pathologic response, patients with CMR had an excellent prognosis in our study.

In our study, there are clinically significant implications. First, CMR can be used to determine the extent of surgery and whether or not to perform surgery. In the absence of these data, it is easy to assume that CMR can also be used as a surrogate for CRS 3. Indeed, we often meet physicians or patients themselves who are reluctant to proceed with IDS on the negative PET/CT scan after NAC. However, our data suggest that the lesion may still have metabolic activity that cannot be assessed by PET/CT, which may eventually lead to CRS 1/2 [10]. We therefore believe that surgery remains a necessary part of the treatment for patients with CMR. Furthermore, the possibility that tumor shrinkage in patients not achieving CRS 3 might enable surgery is important. In contrast, in the non-CMR group, it may be present in lesions with chemo-resistant clones, resulting in the recurrence. A larger tumor burden would remain after NAC in the non-CMR, compared with the CMR group. To reduce the maximal tumor burden, patients with non-CMR may undergo more aggressive surgery. Our data showed that the rate of radical surgery was higher in the non-CMR group; however, they had significantly inferior PFS or OS compared with the CMR group. Therefore, it seems difficult to improve survival with surgery alone, and patients with non-CMR may be candidates for second-line chemotherapy or clinical trials, instead of surgery [27]. Interestingly, in the *BRCA* wild-type group, patients with non-CMR also seem to have a poor prognosis than CMR patients. Therefore, to improve the survival, additional treatments may be considered, especially in *BRCA* wild-type patients with non-CMR after NAC. CA-125 is the only tumor marker recommended as a diagnostic or prognostic indicator and for monitoring of disease recurrence after surgery and adjuvant chemotherapy. In addition, CA-125 normalization at the time of IDS may serve as a surrogate marker for prognosis [28]. Our results showed that CMR after 3 cycles of NAC provides the highest accuracy for predicting platinum-sensitivity, compared with CA-125 normalization before IDS and CRS. In addition, unlike CRS, which is only available after surgery has taken place and the surgical outcome is known, CMR can be used before surgery. This is important because avoiding all invasive interventions that are not beneficial affects the patient's quality of life. Therefore, CMR after NAC may be superior and more suitable to conventional methods such as CA-125.

Our study has some limitations: it was a retrospective and single center study and there might have been a selection bias in patients who underwent serial PET/CT. Small populations with moderate length of follow-up period and immature OS data may also be considered a limitation of the study. Nevertheless, we could find significant associations between the variables and the endpoints in the statistical analyses. This indicates that CMR has the potential to become a widely used tool in imaging of malignancies and deserves to be studied in more detail.

In conclusion, we demonstrated that patients with CMR assessed by ¹⁸F-FDG-PET/CT have a lower rate of recurrence and death compared with patients with non-CMR. CMR is plain and easy to apply in clinical settings. Therefore, CMR after 3 cycles of NAC can be useful for stratifying prognosis in advanced HGSC. A large prospective study with long-term follow-up should be conducted in the future.

ACKNOWLEDGEMENTS

We sincerely thank Young Tae Kim, MD, PhD and Eun Ji Nam, MD, PhD for providing the data.

SUPPLEMENTARY MATERIALS

Table S1

Characteristic of ROC curve for CMR, CA-125 normalization before IDS, and CRS

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Fig. S1

Kaplan-Meier survival curves of PFS (A) and OS (B) according to achievement of CRS 3 in the CMR group.

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Fig. S2

Kaplan-Meier survival curves of PFS (A) and OS (B) according to achievement of CRS 3 in the non-CMR group.

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Fig. S3

Kaplan-Meier survival curves of PFS (A) and OS (B) according to achievement of CMR in patients with *BRCA1/2* wild type.

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Fig. S4

Kaplan-Meier survival curves of PFS (A) and OS (B) according to achievement of CMR in patients with *BRCA1/2* mutation.

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Fig. S5

Kaplan-Meier survival curves of PFS (A) and OS (B) according to achievement CRS.

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Fig. S6

Kaplan-Meier survival curves of PFS (A) and OS (B) according to CA-125 level before IDS.

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