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Original Article

The Pretreatment of Maximum Standardized Uptake Values (SUVmax) of the Primary Tumor Is Predictor for Poor Prognosis for Patients with Epithelial Ovarian Cancer

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The purpose of this study was to evaluate prognostic factors for epithelial ovarian cancer. We found that the pretreatment values of maximum standardized uptake (SUVmax) of the primary tumor by positron emission tomography/computed tomography (PET/CT), tumor marker CA125 and C-reactive protein (CRP) were correlated with clinical characteristics and prognosis for such patients. The clinical parameters and prognoses and their correlations with SUVmax of primary tumor, CA125 and CRP were examined for 51 patients with primary ovarian cancer. The SUVmax of the primary tumor had a statistically significant association with stage ($p = 0.010$) and histology ($p = 0.001$). CA125 was significant associated with stage ($p = 0.011$), histology ($p = 0.005$) and lymph node metastasis ($p = 0.025$). CRP was also significantly associated with stage ($p = 0.049$). Disease-free survival rates of patients exhibiting a high SUVmax, CA125 and CRP were significantly lower than those exhibiting a low SUVmax, CA125 and CRP levels ($p = 0.008$, 0.034, and 0.037, respectively). Furthermore, overall survival rates of patients exhibiting a high SUVmax were significantly lower than those exhibiting a low SUVmax ($p = 0.049$). The high SUVmax of primary tumor is an important factor for identifying ovarian cancer patients with a predictor for poor prognosis.

Key words: ovarian cancer, SUVmax of primary tumor, CA125, C-reactive protein, predictor for poor prognosis

Ovarian cancer is the second most common gynecological malignancy in the United States, accounting for about 21,500 new cases of cancer and 14,600 deaths in the United States in 2009 [1]. Every year in Japan, 8,000 cases of ovarian cancer are newly diagnosed and more than 4,000 women die of the disease [2]. Five-year survival rates are inversely related to the stage of the disease at first diagnosis. The 5-year survival rate for stage I disease is 92.7%. The majority of cases (67-74%), however, are diagnosed with metastatic disease (stage III-IV), which has a 5-year survival rate of only 30.6% [3].

Imaging has become a significant part of the clinical management of patients with ovarian cancer. It is important for tumor detection, staging, and treatment planning. Imaging findings help physicians and oncologists create a specific treatment plan for each individual patient [4]. Metabolic imaging with ^{18}F-FDG PET/CT is a well-established method for the evaluation of primary tumors at the initial, pretreatment stage. PET/CT is superior to CT and MRI for diagnosis of ovarian cancer [5]. In current practice,

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examination of the maximum standardized uptake value (SUVmax) of ^{18}F-FDG PET/CT is one of the most common methods to evaluate primary tumors for the likely clinical outcome. The SUVmax is a unique, noninvasive marker for studying biochemical and metastatic changes in cancer tissues. The SUVmax has been correlated with tumor proliferation rates, tumor grade and expression of glucose transporters, all of which are biomarkers in various types of malignant tumors [6].

A well-characterized biomarker for ovarian cancer is CA125 [7]. Serum CA125 is elevated (*i.e.* > 35 U/ml) in more than 90% of patients with late-stage disease [8]. Its kinetics during chemotherapy has value in predicting residual disease and survival, and levels after therapy can predict recurrence [9]. CA125 levels at clinical presentation are lower in women with mucinous tumors and correlate directly with the stage of disease and inversely with survival [10].

C-reactive protein (CRP) is an acute reactant protein that is increased under various conditions of infection, trauma, tissue necrosis, tumor, and several types of inflammatory disease. Many cancers arise from sites of infection, chronic irritation and inflammation [11]. Evidently, tumor cells co-opt some of the signaling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis [12]. Serum CRP has been investigated as a risk factor and prognostic variable in various human malignancies [13].

It remains uncertain whether the SUVmax of the primary tumor, CA125 and/or CRP are appropriate for predicting outcomes in ovarian cancer. In this study, we evaluated whether pretreatment values of SUVmax of the primary tumor, serum CA125 and serum CRP could serve as prognostic indicators in patients with epithelial ovarian cancer.

Materials and methods

Patients. Fifty-one patients with epithelial ovarian cancer were referred for treatment to the Department of Obstetrics and Gynecology of Okayama University Hospital between April 2007 and September 2010. They underwent PET/CT prior to treatment as part of their initial clinical evaluation. Cancers were staged according to the FIGO staging system, and the local extent of disease was diagrammed on a tumor staging form. The distribution of clinical stages was as follows: 5 stage Ia cancers; 12 stage Ic cancers; 1 stage IIa cancer; 1 stage IIb cancer; 3 stage IIc cancers; 2 stage IIIb cancers; 23 stage IIIC cancers; and 4 stage IV cancers. The histological cell types were classified according to the WHO classification as follows: 29 serous adenocarcinomas; 11 clear cell carcinomas; 4 endometrioid adenocarcinomas; 4 mucinous adenocarcinomas; and 3 mixed type carcinomas (2 serous + endometrioid adenocarcinoma, and 1 mucinous adenocarcinoma + squamous cell carcinoma). Early stage (stage I–II) ovarian cancer patients (n = 22) underwent maximal pelvic/abdominal debulking surgery followed by chemotherapy with carboplatin (Bristol-Myers Squibb, NY, USA) and taxol (Bristol-Myers Squibb, NY, USA). Late-stage (stage III–IV) ovarian cancer patients underwent primary debulking surgery (PDS) (n = 11) and interval debulking surgery (IDS) (n = 18). Patients who underwent PDS or maximal pelvic/abdominal debulking surgery were then treated with six to nine sets of standard chemotherapy. This included 3 to 5 cycles of neoadjuvant chemotherapy with IDS followed by at least 3 cycles of adjuvant chemotherapy. The mean age at the time of treatment was 60.3 years (range, 31–83 years).

PET/CT technique and image analysis. A total of 51 women underwent PET/CT prior to treatment between April 2007 and September 2010 at the Okayama Diagnostic Imaging Center. All patients fasted for at least 5 h before the PET/CT studies. Serum glucose levels measured at the time of ^{18}F-FDG injections were less than 150 mg/dL in all patients. ^{18}F-FDG (3.7 MBq/kg body weight) was administered intravenously into the arm, and the patient was then seated on a chair to rest for 90 min for uptake while drinking 350 ml of mineral water for hydration. A whole body PET/CT scan from the upper end of the orbit to the femoral region was performed 90 min after ^{18}F-FDG administration in the supine position with elevation of the bilateral upper limbs and consisted of 7 to 8 bed positions with 2.4 min per table position. Urinary tract activities were minimized by the placement of a Foley catheter before injection of ^{18}F-FDG and by administration of furosemide and i. v. fluids after injection of ^{18}F-FDG in patients. Images were obtained using a 16-detector row helical PET/CT scanner (Biograph LS/sensation 16, Siemens, Munich, Germany), and were

scatter-corrected and reconstructed using an ordered-subset expectation-maximization (OSEM) iterative reconstruction algorithm with a post-reconstruction Gaussian filter (3 mm full width half maximum). Three-mm-thick sections were obtained from the base of the skull through the proximal thighs at 140 kV, with 12 to 40 m for attenuation data collection and diagnosis.

Image analysis was performed as follows: attenuation-corrected PET images, CT images and co-registered PET/CT images were displayed together on the monitor. The readers had access to all clinical information but were unaware of results from other imaging studies. We also measured the maximum axial diameter (defined as size diagnosis) and SUVmax (defined as SUV diagnosis) of all parenchymatous metastases, lymph node metastases and disseminations with greater FDG uptake than normal organs or surrounding tissue on the FDG-PET/CT images. The cutoff value of SUVmax was the value at which the accuracy was the highest. Size limitations are present since implants < 5 mm are inconsistently identified owing to low tracer concentration and limited spatial resolution [14]. In this case, a short-axis diameter of over 5 mm with positive FDG uptake (SUVmax ≥ 3.0) on PET/CT was considered to be a metastasis. The CT attenuation data were semiquantitatively measured using SUVmax, which was normalized using the lean body mass. For the measurement of FDG uptake, regions of interest (ROI) were manually placed on the main ovary lesion and parenchymatous metastasis, lymph node metastasis and disseminations when abnormal uptakes were observed. SUV was calculated using the following formula:

$$SUV = A/(B/C),$$

where A is the radioactivity concentration in the ROI (in becquerels), B is the injected dose of FDG (in becquerels), and C is the body weight (in grams). The SUVmax is the maximum SUV. The images were evaluated by 2 nuclear-medicine physicians informed about the clinical data of the patient at the time of the scan. Differences in the measurements by the 2 nuclear medicine physicians are not shown.

CA125 and CRP assays. The assays for CA125 and CRP were carried out at the clinical chemistry laboratory at Okayama University Hospital prior to surgery or chemotherapy. The upper limit of normal was 35 U/ml for CA125 and 0.3 mg/dl for CRP.

Statistical analysis. Statistical analyses were performed using the Mann-Whitney U-test for comparisons with the controls and one-factor ANOVA followed by Fisher's protected least significance difference test for all pairwise comparisons. The survival rates were calculated by the Kaplan–Meier method, and the differences between the survival curves were examined by the log-rank test. Analyses were performed using the software package StatView version 5.0 (Abacus Concepts, Berkeley, CA, USA). Differences were considered significant at $p < 0.05$.

Results

In this study, we assessed the association between the pretreatment values of SUVmax of the primary tumor, CA125, CRP, and the clinical parameters and outcomes of ovarian cancers. Fifty-one patients underwent pretreatment assessment of serum CA125 and serum CRP as well as pretreatment imaging. The mean SUVmax on pretreatment imaging of the primary ovarian cancer in the 51 patients was 13.15, with a range of 3.0–28.1. The mean serum CA125 was 1052.24 U/ml, with a range of 17.0–7153 U/ml. The mean serum CRP was 1.67 mg/dl, with a range of 0.01–11.77 mg/dl.

Table 1 shows the distribution of scores for each of the biological parameters examined according to the clinical characteristics in the study population. The SUVmax of the primary tumor showed a statistically significant association with FIGO stage ($p = 0.010$) and histology ($p = 0.001$). CA125 was significant associated with FIGO stage ($p = 0.011$), histology ($p = 0.005$) and lymph node metastasis ($p = 0.025$). CRP was also significant associated with FIGO stage ($p = 0.049$). We assessed the association between SUV max of primary tumor, CA125, CRP and both FIGO stage and tumor histology. However, there was no correlation of the SUVmax of the primary tumor, CA125, or CRP with FIGO stage or histology on ovarian cancer (data not shown).

Late-stage disease (stage III and IV) and serous adenocarcinoma were significantly more frequently associated than early-stage disease and lack of serous adenocarcinoma with high values of SUVmax of primary tumor, CA125, and CRP ($p < 0.005$, $p < 0.005$,

Table 1 Association between SUVmax of primary tumor, CA125, CRP and clinical characteristics of ovarian cancer

Variable	Cases	SUVmax (mean ± SE)	*p*-value*	CA-125 (mean ± SE)	*p*-value*	CRP	*p*-value*
Age (years)			0.729		0.259		0.502
< 60	28	12.90 ± 6.02		815.41 ± 994.77		1.42 ± 2.36	
≥ 60	23	13.45 ± 4.84		1340.56 ± 2000.00		1.95 ± 3.13	
FIGO stage			0.010*		0.011*		0.049*
I + II	22	10.52 ± 4.98		428.07 ± 813.54		1.08 ± 2.11	
III + IV	29	15.15 ± 5.03		1525.75 ± 1785.19		2.12 ± 3.07	
Histology			0.001*		0.005*		0.158
Non serous	22	10.94 ± 4.80		482.05 ± 803.63		0.91 ± 1.53	
Serous	29	14.83 ± 5.43		1484.8 ± 1813.28		2.24 ± 3.26	
Lymph node metastasis			0.147		0.025*		0.114
Negative	35	12.35 ± 5.80		611.74 ± 964.07		1.16 ± 2.21	
Positive	16	14.76 ± 4.47		1933.25 ± 2057.65		2.68 ± 3.37	

*Mann-Whitney U-test. FIGO, International Federation of Gynecology and Obstetrics.
Lymph node status was assessed by PET/CT imaging in 18 patients.

and $p < 0.05$) (Fig. 1A). However, there was no correlation found between the SUVmax of the primary tumor and serum CA125, between the SUVmax of the primary tumor and serum CRP, or between serum CA125 and CRP of primary ovarian cancer (R = 0.155, 0.199, 0.253) (Fig. 1B).

The mean duration of follow-up was 11.4 months (range, 1–38 months). At the time of the last follow-up, 33 patients were alive with no evidence of disease, 8 patients had died of disease, and 10 patients were alive with disease. The mean duration of survival was 14.9 months (range, 1–38 months). Fig. 2 shows the disease-free and overall survival curves of the 51 ovarian cancer patients in relation to the pretreatment SUVmax of the primary tumor, serum CA125, and serum CRP. We divided the pretreatment SUVmax, CA125, and CRP values into high and low groups using the mean values as cut-offs: 13.15, 1052.24 (U/ml), and 1.67 (mg/dl), respectively. The disease-free survival rates of patients exhibiting high SUVmax of the primary tumor, CA125 and CRP were significantly worse than those of patients exhibiting low SUVmax of the primary tumor, CA125 and CRP ($p = 0.008$, 0.034, and 0.037). Moreover, the overall survival rate of ovarian cancer patients exhibiting a high SUVmax of the primary tumor was statistically significantly worse ($p = 0.049$). However, high serum CA125 and CRP were not associated with a diagnosis of a good overall survival rate for the ovarian cancer patient.

Discussion

The pretreatment stage, tumor size, and lymph node status have been recognized as important predictors of patient survival in all cancers. It is accepted that new approaches to ovarian cancers are pivotal in improving treatment of this disease. This is the first study to evaluate the association between the pretreatment SUVmax of primary tumors, serum CA125, serum CRP and clinical factors and prognosis in patients with primary epithelial ovarian cancer.

The presence of abnormal FDG uptake on ^{18}F-FDG PET/CT images has been widely accepted as a criterion for differentiation between benign and malignant disease in various cancers. FDG uptake has been evaluated mainly by visual inspection or calculation of the SUV. A high SUVmax has been shown to correlate with tumor proliferation and with other signs of aggressive tumor behavior including risk of metastasis [15]. Several studies have reported that the SUVmax of the primary tumor is associated with the clinical stage, tumor grade, cell proliferation, and/or glucose metabolism, all of which are reported to be biomarkers for response to chemotherapy and prognosis in ovarian cancer [16, 17].

The serum tumor marker CA125 is used for initial diagnosis and monitoring of response to chemotherapy

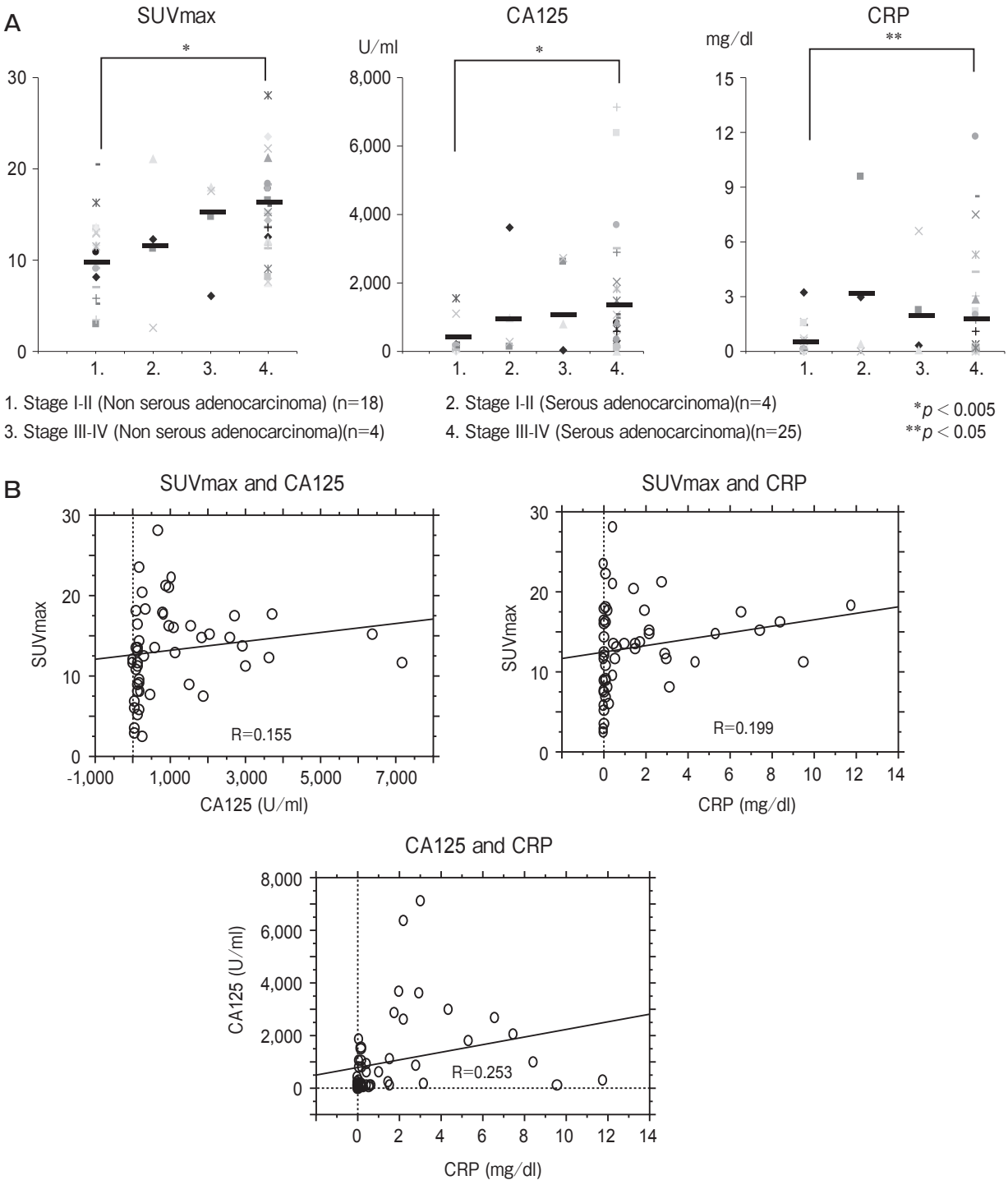

Fig. 1 **A**, Histogram of the SUVmax of the primary tumor, CA125, and CRP expression levels by each stage and histology (1) Early stage (stage I–II) (Non serous adenocarcinoma) (n = 18); (2) Early stage (stage I–II) (Serous adenocarcinoma) (n = 4); (3) Late-stage (stage III–IV) (Non serous adenocarcinoma) (n = 4); (4) Late-stage (stage III–IV) (Serous adenocarcinoma) (n = 25). **B**, Regression analysis of SUVmax of the primary tumor and serum CA125, SUVmax of the primary tumor and serum CRP, serum CA125 and CRP from 51 patients with pretreatment of primary ovarian cancer.

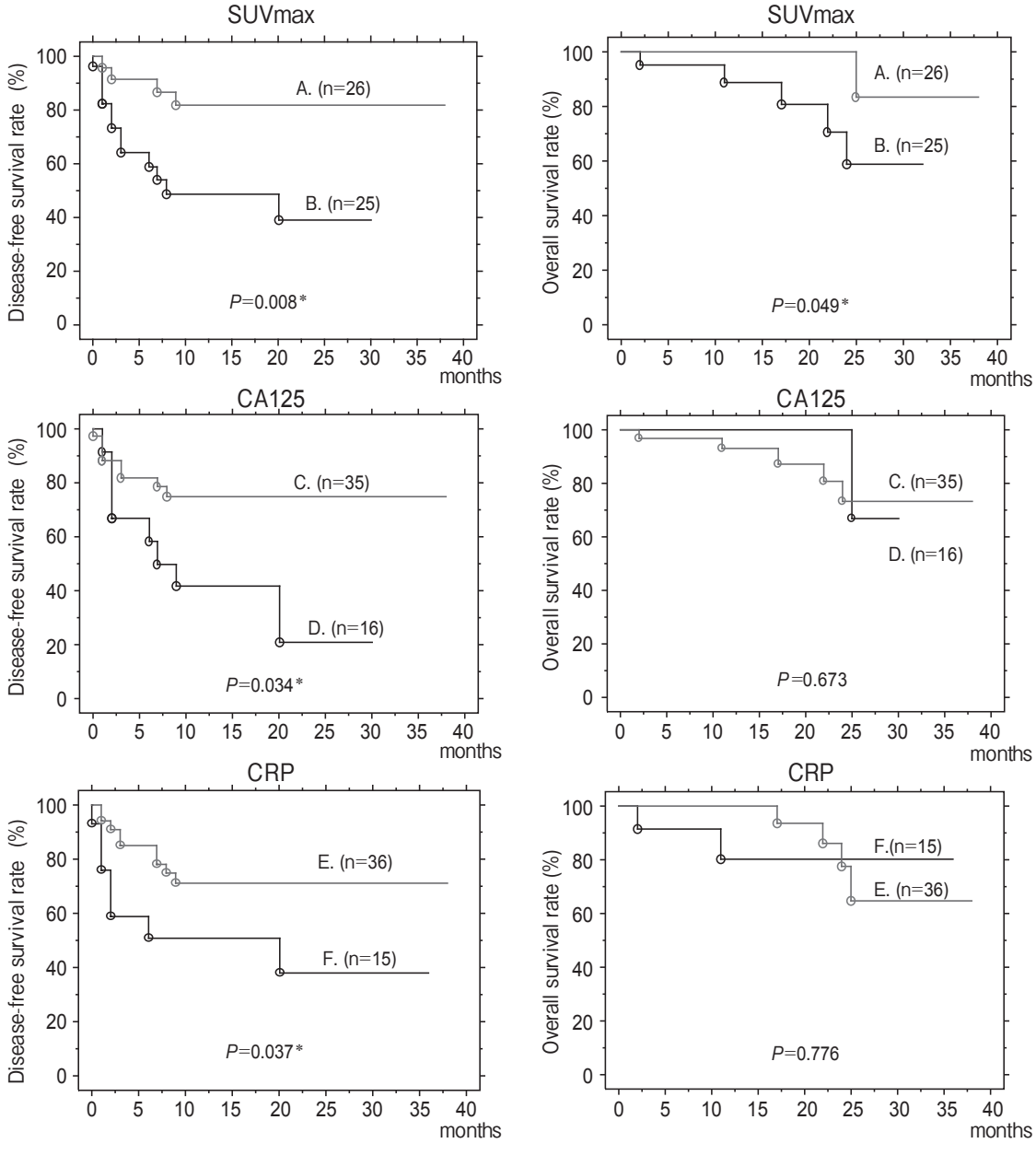

Fig. 2 Kaplan-Meier plots for the disease-free survival and overall survival rates of the 51 patients with pretreatment of primary ovarian cancer according to their SUVmax of primary tumor, serum CA125 or serum CRP. **A**, SUVmax of primary tumor (< 13.15) (n = 26); **B**, SUVmax of primary tumor (≥ 13.15) (n = 25); **C**, Serum CA125 (< 1052.24 U/ml) (n = 35); **D**, Serum CA125 (≥ 1052.24 U/ml) (n = 16); **E**, Serum CRP (< 1.67 mg/dl) (n = 36); **F**, Serum CRP (≥ 1.67 mg/dl) (n = 15).

for epithelial ovarian cancer. Regular measurement during follow-up is one of the best examples in oncology of a test that can detect recurrence of cancer months before symptoms or signs occur [18].

Serum CRP was independently associated with overall survival. This finding is in accordance with other inflammation-related cytokines, such as vascular endothelial growth factor and interleukin-6 [19, 20]. Hefler and colleagues have reported that ovarian cancer patients with a low (≤ 1 mg/dL) serum CRP had significantly better prognoses than those with an elevated (> 1 mg/dL) serum CRP [21].

However, there has been no report in which pretreatment SUVmax of primary tumors and serum biomarkers were measured and correlated with clinicopathological characteristics and prognoses in patients with ovarian cancer. We found that the pretreatment SUVmax of the primary tumor in ovarian cancer patients showed a statistically significant association with FIGO stage and histology. The pretreatment CA125 level was also significantly associated with FIGO stage, histology and lymph node metastasis. CRP was significantly associated only with FIGO stage (Table 1). Furthermore, the present study revealed significantly greater associations of high values for pretreatment SUVmax of the primary tumor, CA125 and CRP with late-stage disease (Stage III or IV) and serous adenocarcinoma than with early-stage disease and non-serous adenocarcinoma (Fig. 1A). However, there was no correlation noted between the pretreatment values of SUVmax of the primary tumor and serum CA125, between SUVmax of the primary tumor and serum CRP, or between serum CA125 and CRP in primary ovarian cancer (Fig. 1B). These were each independent risk factors for ovarian cancer.

This is the first report to associate pretreatment values of SUVmax of the primary tumor, CA125 and CRP with the prognosis of ovarian cancer patients. The high/low cut-off values for SUVmax, CA125, and CRP, as determined by the means, were 13.15, 1052.24 (U/ml), and 1.67 (mg/dl). The disease-free survival rates of patients exhibiting high pretreatment values for SUVmax of primary tumor, CA125 and CRP were significantly lower than those of patients with low SUVmax of the primary tumor, CA125 and CRP for ovarian cancer. Moreover, the overall survival rates of ovarian cancer patients exhibiting high and low SUVmax values of the primary tumor were significantly different (Fig. 2). Taken together, these findings indicate that a high SUVmax of the primary tumor is an important factor for identifying ovarian cancer patients with a poor prognosis.

We acknowledge that there are several limitations to our study. First, the number of patients was relatively small. Second, the duration of follow-up and survival was relatively short. A larger number of patients and longer-term follow-up would improve the quality of our data, and further confirmation by a prospective trial could reinforce our findings.

In summary, there is good evidence that ^{18}F-FDG PET/CT can be useful for the pretreatment assessment of ovarian cancer. We here report our findings that a high (>13.15) pretreatment SUVmax of the primary tumor in patients with ovarian cancer was associated with a poor prognosis.

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