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# Prognostic Significance of Fluorodeoxyglucose Positron Emission Tomography Maximum Standardized Uptake Value in Stage I Ovarian Clear Cell Carcinoma: A Retrospective Observational Study

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## Abstract

**Background: Ovarian clear cell carcinoma (CCC) is often diagnosed at stage I. However, because of the poor prognosis of recurrent cases, even for stage Ia CCC, treatment strategies such as expansion of fertility-sparing treatment and omission of adjuvant chemotherapy have been carefully discussed in recent years. We previously reported the possibility of the maximum standardized uptake value (SUVmax) as a biomarker of CCC prognosis prediction at all stages. In this study, we confirmed differences in SUVmax within stage I CCC and considered treatment strategies. Methods: We selected all 31 patients with ovarian CCC stage I who underwent fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) before treatment between 2006 and 2013 at our institution. This retrospective study was based on their medical records. Results: Clinical tumor stage was Ia in 13 patients, and Ic in 18 (Ic (b) in 11, and Ic (1) + Ic (2) in seven). There were no differences in serum CA125 level, maximum tumor diameter or mural nodules. Median SUVmax was signifi-**

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**cantly higher in stage Ic (5.87) than stage Ia (3.08) cases (*P* = 0.02). Progression-free survival was longer in the low SUVmax group than the high SUVmax group (*P* = 0.08). Conclusions: SUVmax for primary lesions in CCC was significantly higher in stage Ic than stage Ia. As SUVmax represents a prognostic factor in stage I CCC, these findings may suggest SUVmax as an indicator for the application of fertility-sparing surgery and omission of adjuvant chemotherapy for stage Ia CCC.**

## Keywords

**Ovarian Clear Cell Carcinoma, FDG-PET/CT, SUVmax, Biomarker, Prognosis**

## 1. Introduction

Approximately 8000 patients are diagnosed annually with epithelial ovarian cancer and the number has increased in recent years in Japan. Ovarian clear cell carcinoma (CCC) is the second most common histological type after serous adenocarcinoma in Japan. The biological characteristics of epithelial ovarian cancer are known to differ depending on histological type. Serous adenocarcinoma is often diagnosed at advanced stages III and IV; however, CCC is often diagnosed at stage I because of the association of endometriosis with severe adhesion to neighboring organs [1]. In addition, a number of previous studies have suggested that resistance to antineoplastic agents results in the poorer prognosis of patients with this tumor compared with other histological types [2]. Thus, according to the current National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer, the adjuvant chemotherapy recommended for stage Ic disease or greater is recommended to stage Ia CCC cases or above [3]. In addition, although there is a report of fertility-sparing surgery in patients with CCC [4], there is no consensus. With the increase in the number of unmarried nulliparous women, the number of patients with endometriosis-associated CCC is expected to increase. Therefore, treatment strategies for stage I CCC are extremely important. Ovarian cancer is clinically diagnosed on the basis of patient history, serum tumor markers (CA125) and imaging (including fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT)), and confirmed histologically by surgery. In recent years, FDG-PET/CT has been utilized not only for its production of morphological images, but also for its ability to provide information regarding biological functions and metabolism. The maximum standardized uptake value max (SUVmax) of FDG-PET/CT that reflects glucose metabolism of tumors has been reported to be an imaging biomarker for prognostic prediction, therapy evaluation, and chemosensitivity [5]-[8]. We previously reported that the SUVmax of pretreatment primary tumors differs depending on the histological type of epithelial ovarian cancer, that SUVmax is lower in CCC than in serous carcinoma and endometrioid carcinoma, and that SUVmax can be a biomarker to predict prognosis in CCC [5]. When the SUVmax reflects the biological characteristics of the disease, even at stage I CCC, it can be a useful criterion for treatment decisions. In this study, with consideration given to additional indications for fertility-sparing surgery or omission of adjuvant chemotherapy for stage I disease, we focused on the SUVmax of pretreatment stage I ovarian CCC primary tumors and examined the differences within these cases.

## 2. Materials and Methods

### 2.1. Patient Selection and Staging Assessment

For this study, we selected all Japanese patients with ovarian CCC stage I who underwent FDG-PET/CT prior to treatment in our hospital between January 2006 and December 2013 (n = 31). When ovarian cancer was suspected following analysis of patient history and ultrasound and pelvic examinations, FDG-PET/CT was undertaken to enable pretreatment evaluation. CCC was histologically confirmed by surgery. This retrospective comparative study was based on patient medical records for serum CA125 level, FDG-PET/CT (SUVmax) and MRI findings and histopathological diagnosis, and treatment course. For the study of SUVmax as a biomarker to predict prognosis, patients who could be tracked over 3months after their first treatment were divided into two groups based on the median SUVmax to compare survival. Statistical analysis was performed using the Mann-Whitney U test, log-rank test and Pearson's correlation coefficient, and the level of statistical significance was $P < 0.05$. However, the numerical value was listed when a trend was apparent even if $P < 0.09$. As a retrospective and ob-

servational study, cancers were staged according to the Federation of Gynecology and Obstetrics (FIGO) 1988 staging system (**Table 1**) [9]. This study has been approved by the Ethics Committee of Shikoku Cancer Center.

### 2.2. FDG-PET/CT Imaging

Details of the scanning were previously reported [5]. In brief, patients fasted for 4 h before intravenous injection of approximately 3.0 MBq/kg body weight of FDG. The serum glucose level immediately before the injection was measured to ensure a value less than 120 mg/dL. Dual-modality PET/CT imaging was performed using Aquiduo PET/CT (Toshiba Medical Systems Corporation, Otawara, Japan). Whole-body CT scanned the region between the head to the upper thighs, and PET images with attenuation correction were acquired 90 mins later. Acquisition time was adapted according to patient body weight. PET images were scatter-corrected and iteratively reconstructed into a 128 × 128 matrix with 1.34 zooming using interactive algorithms (ordered-subset expectation maximization, two iterations, 14 subsets) and the CT-based attenuation map.

## 3. Results

Median patient age was 54 years (range, 34 - 73 years). Clinical tumor stage was Ia in 13 patients, and Ic in 18 (Ic (b) in 11, and Ic (1) + I (2) in seven) (**Table 2**). All cases were unilateral. Endometriosis coexisted in 26 cases histopathologically. Standard surgery was performed in 22 cases including total hysterectomy, bilateral adnexectomy, greater omentectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy with ascites cytology, and a careful intra-abdominal evaluation. Lymph node biopsies or lymphadenectomy only on the diseased side with total hysterectomy, bilateral adnexectomy, and greater omentectomy were performed in seven cases, including no biopsy without lymphadenopathy. Fertility-sparing surgery was performed in two cases (both cases were stage Ic (b)) including salpingo-oophorectomy on the diseased side of the ovaries, pelvic and para-aortic lymphadenectomy, wedge resection of the remaining ovary and greater omentectomy with cytology of peritoneal washing or ascites. Twenty-seven patients were treated postoperatively with 3 - 6 cycles of adjuvant chemotherapy. Four patients (all stage Ia) did not receive adjuvant chemotherapy owing to the patients' wishes. Three out of 31 patients experienced recurrence and all of them were at stage Ic (2).

**Table 1.** Ovarian cancer staging according to FIGO1988.

| STAGE I: Tumor confined to ovaries | |
|---|---|
| Ia | Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites. |
| Ib | Tumor involves both ovaries otherwise like IA. |
| Ic | Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites. |
| Ic (a) | Capsule rupture before surgery |
| Ic (b) | Surgical spill |
| Ic (1) | Malignant cells in the peritoneal washings. |
| Ic (2) | Malignant cells in the ascites |

**Table 2.** Patient characteristics ($n$ = 31).

| | | n (%) |
|---|---|---|
| Age (median) | | 54 (34 - 73) |
| Stage | Ia | 13 (42%) |
| | Ic(b) | 11 (35%) |
| | Ic(1) | 1 (3%) |
| | Ic(2) | 6 (20%) |
| Unilateral | | 31 (100%) |
| Endometriosis coexist* | | 26 (84%) |

*pathological findings.

There were no differences in serum CA125 level, maximum tumor diameter and mural nodules based on MRI in pathological specimens between stage Ia and Ic (**Table 3**).

The median period from the examination of FDG-PET/CT to surgery was 17.9 days. Median ± standard error of SUVmax for primary lesions was 4.36 ± 0.43 in all 31 patients. Median ± standard error of SUVmax by clinical stage was 3.08 ± 0.49 in stage Ia, and 5.87 ± 0.59 in stage Ic, including 5.4 ± 0.50 in Ic (b) and 6.55 ± 0.78 in Ic (1) + Ic (2). SUVmax tended to increase in proportion to stage, and was significantly higher in stage Ic than Ia ($P$ = 0.02) (**Figure 1**). In addition, SUVmax tended to be higher in stage Ic (1) + Ic (2) cases, in which malignant cells were confirmed in the abdominal cavity, than Ia and Ic (b) (3.81 vs 6.55, $P$ = 0.08). No relationship was evident between SUVmax and serum CA125 level, maximum tumor diameter and mural nodules. A difference in SUVmax was not found regardless of whether endometriosis coexisted or not.

The median duration of follow-up was 60.4 months (range, 2.3 - 104 months).We divided the patients into two groups according to median SUVmax to compare progression-free survival (PFS). PFS tended to be longer in the low SUVmax group than the high SUVmax group ($P$ = 0.08) (**Figure 2**). One patient could not be followed-up.

## 4. Discussion

Approximately 8000 patients are diagnosed with epithelial ovarian cancer each year, of which approximately 4000 patients die, and the number has increased in recent years in Japan. More than half of ovarian cancers are diagnosed at advanced stages III and IV with poor prognosis. Although the introduction of multidrug chemotherapy and molecular-targeted agents has improved survival, the five-year survival rate of advanced ovarian cancer is

**Table 3.** Characteristics of laboratory, imaging and pathological findings*.

| | | Stage Ia | | Stage Ic | | |
|---|---|---|---|---|---|---|
| Serum | CA125 (U/ml) | 25.8 | (12 - 139) | 38.45 | (8 - 3935) | *N.S* |
| MRI | Tumor size (cm) | 10 | (4.2 - 18) | 10 | (5.3 - 15) | *N.S* |
| | Solid part (cm) | 3 | (2 - 10) | 5.1 | (1 - 10.1) | *N.S* |
| Pathological | Tumor size (cm) | 10.5 | (5 - 23) | 15 | (6.5 - 19) | *N.S* |
| findings | Solid part (cm) | 6.7 | (1.5 - 10) | 6 | (1 - 15) | *N.S* |

*median (range).

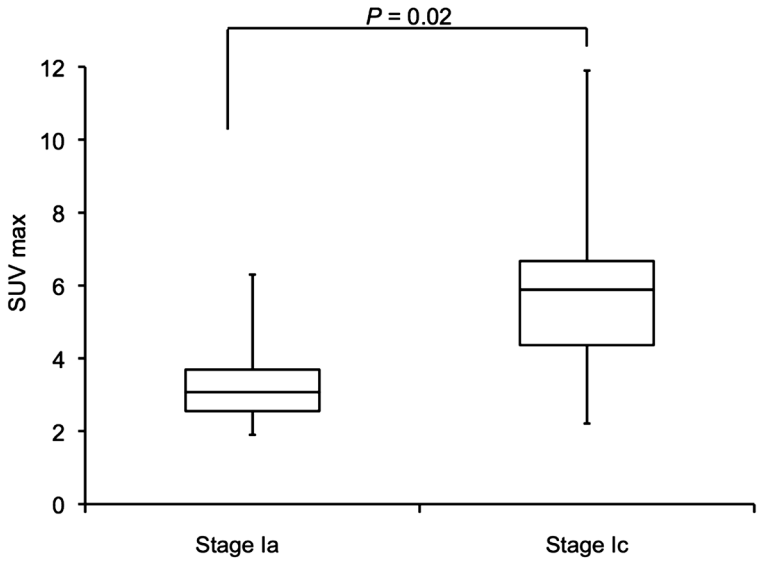


**Figure 1.** Comparison of SUVmax between stage Ia and Ic disease. Box and whisker plot elements are as follows: the length of the box represents the interquartile range, the horizontal line in the box is the median, and the vertical lines issuing from the box extend to the minimum and maximum values.

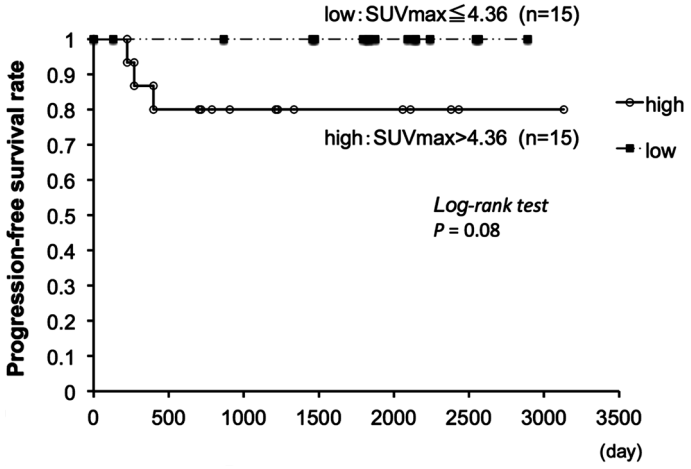


**Figure 2.** Comparison of PFS according to SUVmax.

still 30% to 40%. Prognostic factors of advanced cancer are known to be clinical stage, maximum residual tumor size after surgery, CCC histological type and mucinous carcinoma, older age, and poor performance status [10]-[12]. CCC is rare in Western and Asian nations (3% to 12%), but in Japan it accounts for approximately 22% of all epithelial ovarian cancers, being the second most common histological type following serous carcinoma [13]. However, the reason for the higher incidence in Japan remains unclear. In addition, chemosensitivity is lower in CCC than other histological types, which portends a poor prognosis; thus, clinical studies for individualized treatment strategies are now in progress. Currently, there are high expectations for molecularly-targeted drugs as a new treatment. Up to this point, clinical tests have been conducted for advanced kidney cancer with similar molecular biology [14]. Specifically, mammalian target of rapamycin (mTOR) in the PI3K-AKT pathway is a protein that promotes proliferation, survival, and angiogenesis of cancer cells [15], and the activation rate of mTOR in CCC is higher than in serous carcinoma [16]. The mTOR inhibitor, everolimus, shows antitumor effects both *in vivo* and *in vitro* [16]-[18], and thus, mTOR is expected to be a treatment target.

Conversely, stage I ovarian cancer localized to the ovary accounts for approximately 40% of all ovarian cancers and has a relatively good prognosis. According to the report by the Japan Society of Obstetrics and Gynecology, the five-year survival rate is 95.5% for stage Ia, 79.4% for stage Ic (a), 93.4% for stage Ic (b), 72.9% for stage Ic (1), and 81.4% for stage Ic (2) cases [13]. Currently, some clinical studies for stage I disease are in progress, such as expanding the indication of fertility-sparing treatment (JCOG1203) and omitting adjuvant chemotherapy (JGOG3020). The number of patients with endometriosis is increasing and the number of patients desiring conservative treatment is also increasing because a higher-than-ever number of nulliparous women are in their 30s. Endometriotic cysts have drawn attention as a potential source of ovarian carcinomas such as CCC and endometrioid carcinoma. Furthermore, in CCC, because stage I early-stage cancer accounts for 54.5% of cases, treatment strategies for stage I cases are extremely important. According to the current NCCN guidelines, adjuvant chemotherapy is recommended for stage Ic or greater as well as CCC. However, it is unclear if adjuvant chemotherapy is necessary for stage I, especially stage Ia [19] [20]. In addition, although there is a report of fertility-sparing surgery in patients with CCC [4], there is no general consensus among clinicians. However, some clinical studies are in progress, such as JCOG1203.

Endometriosis is known to be associated with CCC. The most important MRI finding to indicate malignancy accompanying endometriotic cysts of the ovary is the presence of mural nodules protruding from the cyst wall. Tanaka *et al*. reported that the mean maximum cyst diameter was 7.8 cm (range, 3.2 - 14.2 cm) in benign cases and 11.2 cm (range, 4.0 - 19.2 cm) in malignant cases [21]. In addition, the mean maximum diameter of the mural nodules was 1.2 cm (range, 0.4 - 2.3 cm) in benign lesions and 4.3 cm (range, 1.0 - 8.7 cm) in malignant lesions. Both diameters were also significantly larger in the malignant group [21]. However, there is no examination within stage I ovarian cancer cases. The diameters of tumor and mural nodules in this previous study were similar to our findings, and there was no significant difference between stage Ia and Ic cases; tumor diameter and mural nodule diameter did not appear to differ significantly between stage Ia and Ic.

In general, malignant tumors have enhanced glucose metabolism, and FDG-PET/CT exploiting this characte-

ristic has become common in recent years for diagnosis of malignant tumors [22]-[25]. In ovarian cancer, FDG-PET/CT is used for pretreatment imaging to define tumor extent. Furthermore, SUVmax has recently been reported as a biomarker of prognosis prediction and therapy evaluation. With epithelial ovarian cancer, it has been reported that SUVmax is higher in advanced cancer compared with early-stage cancer [26]. We also reported that the five-year survival rate for CCC tended to be higher in the low SUVmax group than in the high SUVmax group, and that SUVmax could be considered to be a prognostic factor [5]. In this study, within stage I, the low SUVmax group had prolonged PFS compared with the high SUVmax group, which was similar to our previous study results. Because of the low recurrence rate of stage I CCC, there were no significant differences between these two groups. However, it is worth accumulating more cases and conducting further examinations. In addition, it has been reported that in renal cell carcinoma, there was a positive correlation between AKT and SUVmax, and a higher SUVmax and increased expression of AKT were associated with shorter overall survival [27]. These findings reflect our previous study results for CCC. Also, since there is a positive correlation between AKT and SUVmax, a similar trend is expected for mTOR and SUVmax, and high mTOR activity is assumed to show high SUVmax; therefore, SUVmax is expected to be a marker of drug sensitivity. Cases with high mTOR activity have high sensitivity to mTOR inhibitor [28], and it has been reported that SUVmax was decreased by inhibitingmTOR [29]. We built a hypothesis based on the above results, that ovarian CCC with low SUVmax may often be diagnosed at stage Ia, have a good prognosis, and exhibit low sensitivity to mTOR inhibitor, indicating that mTOR inhibitor is not expected to be effective.

In this study, we compared the SUVmax of primary tumors at stage I CCC, in which expansion of the indication for fertility-sparing treatment and omission of adjuvant chemotherapy have been discussed. SUVmax was significantly higher in stage Ic than stage Ia, which indicated that biological characteristics such as glucose metabolism differed even within stage I. These results are considered to support the omission of adjuvant chemotherapy and fertility-sparing surgery for stage Ia CCC in the future from the perspective of glucose metabolism. We acknowledge that there are several limitations to our study. First, the number of patients was relatively small. Second, this was a retrospective study at a single institution; however, conversely, because SUV is a semi-quantitative index and may vary from one PET center to another, a single institution study was a strong point. 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. The possibility of SUVmax as a biomarker for treatment strategy decision needs to be further investigated.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## Research Involving Human Participants and/or Animals

This article does not include any studies performed on human participants or animals.

## Informed Consent

Formal consent is not required for this type of study.

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