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Clinical significance of initial symptoms in endometriosis-associated ovarian cancer

Endometriozis ile ilişkili over kanserinde başlangıç semptomlarının klinik önemi

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Abstract

Objective: Endometriosis is associated with various symptoms, but their severity varies from case to case. In this study, we investigated the reality of symptoms presented by patients with clinically early-stage endometriosis-associated ovarian cancer (EAOC) and explored the relationship between symptoms and laboratory/imaging findings, pathological findings, and prognosis.

Materials and Methods: This was a retrospective case-control study of patients who received initial surgical treatment and were diagnosed with clinically early-stage EAOC, including ovarian endometrioid carcinoma (OEC), ovarian clear cell carcinoma (OCCC), and seromucinous borderline tumor (SMBT). Patients with OEC/OCCC diagnosed between 2006 and 2016 and those with SMBT diagnosed between 2006 and 2020 were included. Chi-square and Kaplan-Meier estimates were used for statistical analyses.

Results: One hundred-seven patients (OEC, n=31; OCCC, n=39; SMBT, n=37) were included. Fifty-nine (55.1%) patients presented with symptoms, and the proportion of patients with OEC who presented with symptoms was significantly higher than that of others (OEC, 77.4%; OCCC, 43.6%; SMBT, 48.6%). The details of symptoms differed significantly among the pathological types (lower abdominal pain/abdominal discomfort/abnormal bleeding, OEC: 11/8/9; OCCC: 6/12/1; SMBT: 15/5/3). Only in the OEC group did symptomatic patients show significantly higher white blood cell (WBC) count and neutrophil/lymphocyte (N/L) ratio (symptomatic vs. asymptomatic, median: WBC count: 7250 vs. 5000, p=0.008; N/L ratio: 4.6 vs. 1.7, p=0.013). None of the asymptomatic patients showed recurrence during follow-up.

Conclusion: Patients with EAOC show varying symptoms depending on the histological type of the tumor. Laboratory findings underlying symptoms also vary by histopathological type, which may reflect differences in the carcinogenesis process.

Keywords: Adenocarcinoma, clear cell/carcinoma, endometrioid/carcinoma, ovarian epithelial/endometriosis, inflammation, signs and symptoms

Öz

Amaç: Endometriozis çeşitli semptomlarla ilişkilidir ancak bunların şiddeti hastadan hastaya değişir. Bu çalışmada, klinik olarak erken evre endometriozis ile ilişkili yumurtalık kanseri (EAOC) olan hastaların semptomlarının gerçekliğini araştırdık ve semptomlar ile laboratuvar/görüntüleme bulguları, patolojik bulgular ve prognoz arasındaki ilişkiyi araştırdık.

Gereç ve Yöntemler: Bu çalışma, başlangıçta cerrahi tedavi alan ve yumurtalık endometrioid karsinomu (OEC), yumurtalık berrak hücreli karsinomu (OCCC) ve seromüsinöz borderline tümör (SMBT) dahil olmak üzere klinik olarak erken evre EAOC tanısı konan hastaları içeren retrospektif bir olgu kontrol çalışmasıydı. Bu çalışmaya 2006-2016 yılları arasında OEC/OCCC tanısı konulan hastalar ve 2006-2020 yılları arasında SMBT tanısı konulan hastalar dahil edildi. İstatistiksel analizlerde ki-kare ve Kaplan-Meier tahminleri kullanıldı.

Bulgular: Yüz yedi hasta (OEC, n=31; OCCC, n=39; SMBT, n=37) dahil edildi. Elli dokuz (%55,1) hasta semptomla başvurdu ve semptomla başvuran OEC'li hastaların oranı diğerlerine göre anlamlı derecede yüksekti (OEC, %77,4; OCCC, %43,6; SMBT, %48,6). Semptomların ayrıntıları patolojik tipler

PRECIS: Initial symptoms differ according to several histological types in endometriosis-associated ovarian cancer. A detailed elucidation of clinical symptoms may lead to a better understanding of individual cancer biology.

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arasında anlamlı farklılık gösteriyordu (karın alt kısmında ağrı/karın rahatsızlığı/anormal kanama, OEC: 11/8/9; OCCC: 6/12/1; SMBT: 15/5/3). Yalnızca OEC grubunda semptomatik hastalarda anlamlı derecede yüksek beyaz kan hücresi (WBC) sayısı ve nötrofil/lenfosit (N/L) oranı görüldü (semptomatik vs. asemptomatik, medyan: WBC sayısı: 7250 vs. 5000, p=0,008; N/ L oranı: 4,6'ya karşı 1,7, p=0,013). Asemptomatik hastaların hiçbirinde takip sırasında nüks görülmedi.

Sonuç: Erken evre endometriozis ile ilişkili yumurtalık kanserli hastalar tümörün histolojik tipine bağlı olarak değişen semptomlar göstermektedir. Semptomların altında yatan laboratuvar bulguları da histopatolojik tipe göre değişiklik gösterir ve bu da karsinogenez sürecindeki farklılıkları yansıtabilir.

Anahtar Kelimeler: Adenokarsinom, berrak hücreli/karsinom, endometrioid/karsinom, yumurtalık epitelyal/endometriozis, enflamasyon, belirti ve semptomlar

Introduction

Endometriosis is a common gynecological disorder. In addition, it is a known precursor of malignant tumors. Endometriosis-associated ovarian cancer (EAOC) is a particularly distinct subtype of ovarian cancerderived from ovarian endometriosis[1-3]. A large proportion of EAOC cases are clinically International Federation of Gynecology and Obstetrics (FIGO) stage I cases, in which the lesions are clinically confined to the ovaries[4-6]. In general, FIGO stage I ovarian cancer is not considered to have a poor prognosis[7]; however, there are some differences among different histopathological types. Ovarian clear cell carcinoma (OCCC) and ovarian endometrioid carcinoma (OEC) are representative histological subtypes of EAOC[8,9]. Seromucinous borderline tumor (SMBT), which is not strictly a cancer but a borderline malignancy, is also known to occasionally arise from endometriosis[10].

Because SMBT is considered a borderline malignancy, its prognosis is good[11]. On the other hand, OEC and OCCC are more malignant than SMBT. Nevertheless, the omission of postoperative chemotherapy is being considered for some FIGO stage I OEC cases[12]. OCCC is particularly known to have a poor prognosis that is associated with platinum resistance[9]. Aggressive surgical procedures, such as combined resection of the tumor with other organs, may be considered for complete pathological resection of the tumor. from the same endometriosis, a variety of tumors can arise that differ greatly in their phenotype.

Recently, several reports have examined the differences in terms of genetic alteration among various histologic types of EAOC. However, to our knowledge, few studies have focused on the differences in clinical symptoms due to differences in histology. Ovarian cancer has long been generally believed to not present symptoms until advanced stages[13]. However, a recent report indicated that 72% of patients with high-risk early-stage ovarian cancer show physical symptoms at the time of initial presentation[14]. Originally, endometriosis was associated with various symptoms, such as dysmenorrhea, which sometimes reduces daily quality of life[15]. However, the severity of symptoms varies widely from case to case, and asymptomatic cases do arise[16]. Therefore, we hypothesized that symptoms of patients with EAOC can also vary from patient to patient, which may be reflected in histological differences. Although several epidemiological studies have indicated that a history of severe menstrual pain[17,18], suggesting the presence of endometriosis, may increase the risk of ovarian cancer, few studies have investigated the initial symptoms of patients with EAOC in detail.

Thus, the aim of this study was to investigate the clinical significance of the initial symptoms of OEC, OCCC, and SMBT, which are frequently encountered EAOC subtypes, in FIGO stage I cases with lesions confined to the ovaries. In addition, we sought to identify the symptoms that were present at the time of the initial examination and explored the relationship between these symptoms and laboratory, imaging, and pathological findings and prognosis.

Materials and Methods

Patients

This case-control study included patients with OEC, OCCC, and SMBT who underwent initial treatment at our institution. For OEC and OCCC, we included patients clinically diagnosed with FIGO[19] stage I disease who underwent initial surgery between 2006 and 2016. For SMBT, we included patients clinically diagnosed with FIGO stage I disease who underwent initial surgery between 2006 and 2020. Patients whose postoperative clinical course could not be followed for more than one year were excluded; however, no such patients were found. We then compared several factors among the three groups.

Ethics Approval and Consent to Participate

This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (approval number: G531, date: 29.09.2023) and conforms to the Declaration of Helsinki. Informed consent was obtained from all participants via an opt-in approach (wherein participants signed a printed informed consent document) or an opt-out approach (wherein participants were informed about the study through the website).

Evaluation of Clinical Symptoms

Clinical data were extracted from patients' medical records and collected through in-person interview questionnaires. First, we investigated whether the patients reported symptoms or not. If they did, we investigated the details of the symptoms reported and categorized them into several groups according to frequency. A detailed review of patients who showed symptoms revealed that the symptoms could be divided into three categories: abdominal pain, abdominal discomfort (fullness or increased

abdominal girth), and abnormal bleeding. As it is difficult to assume the degree of these symptoms, we qualitatively assessed their presence or absence. Thereafter, we examined the correlation between the symptoms, clinical course of the disease, and laboratory and imaging findings of the patients. This study first examined each of the three histological types of EAOC. A subgroup analysis was also conducted separately for premenopausal and post-menopausal status.

Assessment of Clinical and Laboratory Findings

Information on clinical, laboratory, and imaging findings were extracted from the patients' medical records, including age at the time of initial treatment, white blood cell (WBC) count in the peripheral blood immediately before initial treatment, neutrophil/lymphocyte ratio (N/L-R), serum CA125 level, and maximum tumor diameter. The CA125 values were log-transformed (log-CA125) and used for analysis. The maximum tumor diameter was measured using imaging findings. All patients underwent surgical treatment, and the FIGO stage, assigned based on intraoperative and pathological findings, was evaluated as well. Tumor progression was classified into two groups: the capsuled group (C group; FIGO stages IA, IB, and IC1), which comprised patients whose tumors had not reached the ovarian serosa at the start of surgery, and the uncapsuled group (un-C group; FIGO stages IC2, IC3, and IIIA1), which included patients whose tumors had progressed beyond the ovarian surface. Data regarding recurrence and death from the primary disease were also extracted and analyzed.

Statistical Analysis

Differences in continuous and categorical variables between the two groups were compared using the unpaired t-test and Fisher's Exact test or chi-square test, respectively. Differences in continuous and categorical variables among more than three groups were compared using one-way analysis of variance and Fisher's Exact test, respectively. When significant differences were observed between the groups, post hoc pairwise comparisons were performed using the t-test with Bonferroni correction. $P<0.05$ was considered statistically significant in each analysis, except for the variables analyzed using Bonferroni correction. Kaplan-Meier survival plots based on presenting symptoms were calculated and compared using the log-rank test. All statistical analyses were performed using PRISM version 9.0 (GraphPad Software, San Diego, CA, USA).

Results

Symptoms of Stage I EAOC

One hundred-seven patients with EAOC were included in this study. Of these, 31 patients (29.0%) had OEC, 39 (36.4%) had OCCC, and 37 (34.6%) had SMBT. The age distribution of the patients according to histological type, FIGO classification based on pathological findings, pathological presence of endometriosis, and presence of endometrial disorders are shown in Table 1. Among the 107 patients, 59 (55.1%) experienced at least one symptom. Abdominal pain was the most common symptom (32 patients, 29.9%), followed by abdominal discomfort (25 patients, 23.3%) and abnormal bleeding (13 patients, 12.1%). Of the 59 symptomatic patients, 48 (81.3%) had only one of these symptoms, whereas 11 (18.6%) experienced multiple symptoms (Table 2A).

Symptoms were not statistically associated with menopausal status; however, they were associated with histological subtype. The presentation of symptoms was most common in the OEC group, with 24 (77.4%) of the 31 patients presenting with any of the three above-mentioned symptoms. Eighteen (48.6%) of the 37 patients in the SMBT group presented with symptoms, whereas 17 (43.6%) of the 39 patients in the

Table 1. Demographic and pathological characteristics of participants

	OEC	OCCC	SMBT
Number	31	39	37
Age	50.0 (41.0-58.0)	52.0 (44.0-64.0)	42.0 (34.5-52.5)
FIGO-stage			
IA	8 (25.8%)	15 (38.5%)	30 (81.1%)
IB	1 (3.2%)	0 (0.0%)	2 (5.4%)
IC1	13 (41.9%)	13 (33.3%)	5 (13.5%)
IC2	5 (16.1%)	6 (15.4%)	0 (0.0%)
IC3	4 (12.9%)	4 (10.3%)	0 (0.0%)
IIIA1(i)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Presence of endometriosis (pathologically)	27 (87.1%)	30 (76.9%)	28 (75.7%)
Neoplasm in endometrium	10 (32.3%)	0 (0.0%)	0 (0.0%)

OEC: Ovarian endometrioid carcinoma, OCCC: Ovarian clear cell carcinoma, SMBT: Seromucinous borderline tumor, FIGO: Federation of Gynecology and Obstetrics

OCCC group showed symptoms (Table 2B, p=0.011). Analysis of the symptoms showed that lower abdominal pain was the most common symptom in the OEC group (11 patients, 35.5%). However, nine patients (29.0%) in the OEC group also presented with abnormal bleeding, whereas eight patients (25.8%) reported lower abdominal discomfort, indicating that the frequency of each symptom in the OEC group was almost equal. In the OCCC group, the most common symptom was lower abdominal discomfort (12 patients, 30.8%), followed by lower abdominal pain (six patients, 15.4%) and abnormal bleeding (one patient, 2.6%). In the SMBT group, the most common symptom was lower abdominal pain (15 patients, 40.5%), followed by lower abdominal discomfort (five patients, 13.5%) and abdominal bleeding (three patients, 8.1%). There was a significant difference in the distribution of symptoms among the three groups (Table 2C). The OEC group showed an even distribution of symptoms. In contrast, the OCCC group showed a tendency toward lower abdominal discomfort, whereas the SMBT group showed a tendency toward lower abdominal pain.

Differences in Physical Symptoms Among Patients with Stage I OEC, OCCC, and SMBT

We then divided the patients into two groups, pre- and post-menopausal status and conducted a subgroup analysis (Figure 1). The results showed that in the OEC group, 12 of the

Table 2. The analyses about the frequency of symptoms and their background
A. The frequency of the presence of symptoms and its details

	Num	Distribution (%)	95% CI*
No. of symptoms			
0 (No symptoms)	48	44.9	35-55
1 (1 symptom)	48	44.9	35-55
More than 1 (multiple symptoms)	11	10.3	5-18
Symptom description			
Abdominal pain	32	29.9	21-40
Abdominal discomfort	25	23.4	16-33
Abnormal bleeding	13	12.1	7-20

OEC: Ovarian endometrioid carcinoma, OCCC: Ovarian clear cell carcinoma, SMBT: Seromucinous borderline tumor, *Calculated by Clopper-Pearson exact method, CI: Confidence interval

Table 2. The analyses about the frequency of symptoms and their background
B. Comparison among age groups and histologies

	No symptoms	With symptoms	p-value
Menopause status			
Premenopausal status	27	31 (53.4%)	0.130
Postmenopausal status	30	19 (38.8%)	
Histology			
OEC	7	24 (77.4%)	0.011
OCCC	22	17 (43.6%)	
SMBT	19	18(48.6%)	

OEC: Ovarian endometrioid carcinoma, OCCC: Ovarian clear cell carcinoma, SMBT: Seromucinous borderline tumor

Table 2. The analyses about the frequency of symptoms and their background
C. Comparison among histologies as for the details of symptoms

	OEC	OCCC	SMBT	p-value
Bleeding	9 (29.0%)	1 (2.6%)	3 (8/1%)	
Abdominal discomfort	8 (25.8%)	12 (30.8%)	5 (13.5%)	
Abdominal pain	11 (35.5%)	6 (15.4%)	15 (40.5%)	0.0089

OEC: Ovarian endometrioid carcinoma, OCCC: Ovarian clear cell carcinoma, SMBT: Seromucinous borderline tumor

16 patients (75.0%) with premenopausal status and 12 of the 15 patients (80.0%) with postmenopausal status experienced some symptoms. There was no difference in the frequency of symptoms; however, there were differences in the symptom distribution between the two age groups. Patients with premenopausal status mainly reported a single symptom, with lower abdominal pain being the most common symptom (eight patients, 50.0%), followed by lower abdominal discomfort (four patients, 25.0%) and abnormal bleeding (three patients, 18.8%). On the other hand, postmenopausal patients most frequently reported abnormal bleeding (six patients, 40.0%), followed by lower abdominal discomfort (four patients, 26.7%) and abdominal pain (three patients, 20.0%). In the OCCC group, lower abdominal discomfort was the most common complaint in both the premenopausal and postmenopausal status groups. However, the frequency of symptoms significantly differed between the two groups. Only 3 of 15 patients (20.0%) in the premenopausal status presented symptoms, while 14 of 24 (58.3%) patients in the postmenopausal status presented with symptoms. The SMBT group showed the highest frequency of complaints of lower abdominal pain for those in both premenopausal and postmenopausal status. However, 16 of the 27 patients (59.3%) in the premenopausal status presented with symptoms, whereas only two of 10 patients (20.0%) in the postmenopausal status showed symptoms. The OEC, OCCC, and SMBT groups differed in terms of the frequency of symptoms, menopausal status, and distribution of symptoms.

Clinical Significance of Physical Symptoms of OEC, OCCC, and SMBT

The correlation between the presence of symptoms and laboratory, imaging, and pathological findings for each histological subtype of EAOC was analyzed. The results are presented in Table 3. In the OEC group, symptomatic patients showed significantly higher WBC count, N/L-R, and log-CA125 than asymptomatic patients [symptomatic vs. asymptomatic (median): WBC count: 7.25 vs. 5.00, p=0.008; N/L-R: 4.6 vs. 1.7, p=0.013; log-CA125: 8.8 vs. 5.8, p=0.0014, respectively, Table 3A]. Symptomatic patients tended to show slightly larger maximum tumor diameter than asymptomatic patients; however, the difference was not significant (median: 11.0 cm vs. 6.4 cm for symptomatic and asymptomatic patients, respectively; p=0.15, Table 3A). Regarding tumor progression, more symptomatic patients (eight of 24) than asymptomatic patients (one of seven) were in the un-C group; however, this difference was not significant (p=0.64). The symptomatic patients were divided into an abnormal bleeding group and a non-abnormal bleeding group (lower abdominal pain or lower abdominal discomfort) for further analysis (Supplementary Table 1). The results showed that there was no difference between the abnormal and non-abnormal bleeding groups. Regarding the frequency of endometrial disorders, 4 of 9 patients (44.4%) in the abnormal bleeding group and in five of 15 patients (33.3%) in the non-abnormal bleeding group had endometrial disorders.

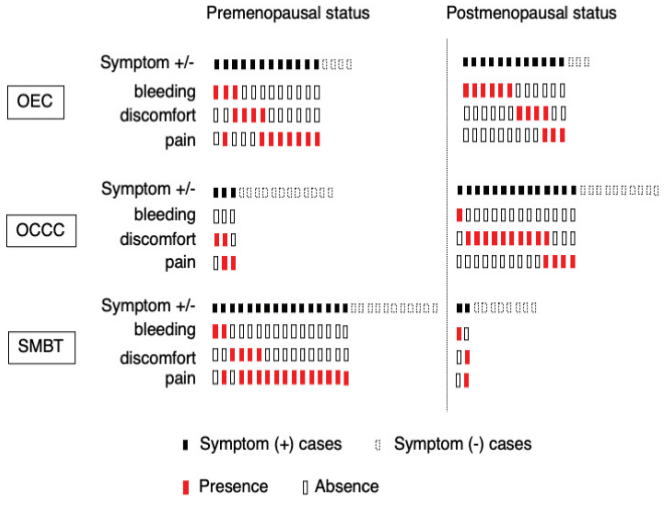

Figure 1. Distribution of clinical symptoms in each case

OEC: Ovarian endometrioid carcinoma, OCCC: Ovarian clear cell carcinoma, SMBT: Seromucinous borderline tumor

In the OCCC group, there were no differences in WBC count or N/L-R between symptomatic and asymptomatic patients [symptomatic vs. asymptomatic (median): WBC count: 6.80 vs. 5.88, p=0.17; N/L-R: 2.5 vs. 2.4, p=0.23, respectively, Table 3B]. However, the symptomatic patients showed significantly higher log-CA125 and larger maximum tumor diameter than the asymptomatic patients [symptomatic vs. asymptomatic (median): log-CA125: 5.3 vs. 4.3, p=0.033; maximum tumor diameter: 15.0 vs. 7.9, p=0.0013; respectively, Table 3B]. Regarding tumor progression, nine of 17 symptomatic patients (52.9%) and two of 22 (9.1%) asymptomatic patients were in the un-C group. The difference in the frequency of tumor progression between symptomatic and asymptomatic patients was significant (p=0.0098, Table 3B).

In the SMBT group, the only significant difference between symptomatic and asymptomatic patients was the maximum tumor diameter [symptomatic vs. asymptomatic (median): 9.7 vs. 4.9, p=0.0011, Table 3C]. As all patients in the SMBT group had stage IC1 disease or lower, the presence or absence of intraoperative tumor rupture was examined; however, there was no significant difference in the presence or absence of intraoperative tumor rupture between the symptomatic and asymptomatic patients (1 of 18 symptomatic patients, 5.6% vs. 4 of 19 asymptomatic patients, 21.1%; p=0.17; Table 3C).

We then examined whether the presence or absence of symptoms was a predictor of poor prognosis in OEC and OCCC. The results showed that all asymptomatic patients in both the OEC and OCCC groups survived without recurrence (Supplementary Figure 1). Three of 24 symptomatic patients (12.5%) with OEC and four of 17 symptomatic patients (23.5%) with OCCC died of the disease after recurrence. Most of the deceased cases had uncapsule status; however, one of

the deceased cases in the OCCC group was pathologically confirmed to have stage IA disease after systematic lymph node dissection was performed (Supplementary Figure 1).

Discussion

In this study, we examined the presence and details of physical symptoms at the time of initial diagnosis of EAOC, which is often diagnosed in patients with diseases confined to the ovary. The results showed that among patients with EAOCs, those with OEC presented with symptoms most frequently (77%). In particular, abnormal bleeding was the most common initial symptom in postmenopausal patients with OEC. Postmenopausal patients may be more likely to notice even small amounts of abnormal bleeding, which may have resulted in a higher incidence of initial symptoms in patients with OEC. The fact that abnormal bleeding was particularly common among patients with OEC in this study is a prominent finding. Lurie et al.[20]. reported that patients with endometrioid carcinoma were three times more likely to present abnormal bleeding compared with patients with serous carcinoma. Lurie et al.[21] also reported that patients with localized endometrioid carcinoma were more likely to present with abnormal bleeding compared with patients with localized clear cell carcinoma. In cases of suspected ovarian malignancy with a background of endometriosis, OEC should be considered if the patient presents with abnormal bleeding. Several studies have demonstrated

Table 3. Comparison of clinic-pathological factors between symptom+ and symptom-
A. Analyses in patients with OEC

	Symptom (+)	Symptom (-)	p-value
WBC (x10^3/uL)	7.25 (5.70-10.2)	5.00 (3.30-8.50)	0.0078
N/L ratio	4.6 (2.4-7.1)	1.7 (1.0-6.5)	0.013
CA125 (log-scale)	8.8 (6.4-9.7)	5.8 (3.6-7.0)	0.014
Size (cm)	11 (7.2-13.0)	6.4 (4.5-16.5)	0.15
Capsuled group	16	6	
Un-capsuled group	8	1	0.64

OEC: Ovarian endometrioid carcinoma, WBC: White blood cell, N/L: Neutrophil/lymphocyte

Table 3. Comparison of clinic-pathological factors between symptom+ and symptom-
B. Analyses in patients with OCCC

	Symptom (+)	Symptom (-)	p-value
WBC (x10^3/uL)	6.80 (4.46-8.91)	5.88 (4.67-7.18)	0.17
N/L ratio	2.5 (1.8-4.9)	2.4 (2.1-3.6)	0.23
CA125 (log-scale)	5.3 (4.7-7.6)	4.3 (4.0-5.0)	0.033
Size (cm)	15.0 (12.0-16.0)	7.9 (5.5-10.7)	0.0013
Capsuled group	8	20	
Un-capsuled group	9	2	0.0098

OEC: Ovarian endometrioid carcinoma, WBC: White blood cell, N/L: Neutrophil/lymphocyte

Table 3. Comparison of clinic-pathological factors between symptom+ and symptom-
C. Analyses in patients with SMBT

	Symptom (+)	Symptom (-)	p-value
WBC (x10^3/uL)	5.72 (5.27-7.00)	5.59 (4.95-6.44)	0.37
N/L ratio	2.3 (1.7-3.5)	2.4 (1.5-3.6)	0.78
CA125 (log-scale)	6.1 (4.9-7.6)	5.1 (4.0-6.5)	0.32
Size (cm)	9.7 (7.0-11.2)	4.9 (4.0-6.6)	0.0011
p-stage IA/B	17	15	
p-stage IC	1	4	0.17

OEC: Ovarian endometrioid carcinoma, WBC: White blood cell, N/L: Neutrophil/lymphocyte

that when endometriosis is present, synchronous tumors often develop in the endometrium and ovaries, with endometrioid carcinoma being the most common histological type[1,22]. In the present study, endometrial disorders were detected in 10 of 31 patients with OEC but not in patients with OCCC and SMBT, which may be a cause of abnormal bleeding in patients with OEC. However, not all cases of abnormal bleeding had endometrial disorders, suggesting the possibility of other reasons.

In this study, we further analyzed the details of the symptoms presented by patients with OEC, OCCC, and SMBT. We found that symptomatic patients with OCCC and SMBT had significantly larger tumors than asymptomatic patients, whereas there was no significant difference in tumor size between symptomatic and asymptomatic patients with OEC. Chan et al.[14] reported that approximately 72% of patients with early-stage high-grade tumors, including OCCC but not OEC, confined to the ovary were symptomatic, and their symptoms were associated with tumor size. The results of the present study are comparable with these findings. For OEC, however, the correlation between the presence of symptoms and tumor size was not as strong as that for OCCC or SMBT. Instead, WBC count and N/L-R were strongly associated with the absence of any symptoms, including abnormal bleeding, in patients with OEC. The elevation of both WBC count and N/L-R in patients with OEC suggests a correlation between inflammation and a variety of physical symptoms, including abdominal pain, abdominal discomfort, and abnormal bleeding. We speculate that these differences in the symptom background may reflect differences in the nature of the tumors.

Recent research has rapidly progressed in identifying genetic alterations in cancer cells, and several genetic pathways that are characteristic of SMBT, OCCC, and OEC have been reported. OEC is associated with many genetic changes that are strongly correlated with inflammation[23,24]. Considering the strong correlation between elevated WBC count and N/L-R and the presence of physical symptoms in patients with OEC, it is possible that a persistent inflammatory state is closely related to the development of OEC and the presence of symptoms. The various physical symptoms and high frequencies associated with OEC may reflect a persistent inflammatory response between the ectopic endometrial tissue and the surrounding tissue, which is also a factor in carcinogenesis. Regarding OCCC, several studies have demonstrated that the tumor is associated with specific oncogenic alterations, such as strong involvement of HNF1B and the SWI/SNF complex, including ARID1A[25]. For SMBT, KRAS, a known oncogene, is involved in almost all cases of SMBT[26]. Considering that in the present study, the frequency of symptoms among patients with OCCC and SMBT increased with increasing tumor size, it is likely that patients with OCCC and SMBT are symptomatic only when malignant tumors grow sufficiently because of signal changes, rather than being symptomatic because of interactions in the microenvironment. However, this retrospective observational study has limitations. In addition to the limited number of cases, the inability to ask detailed questions about symptoms systematically is another limitation of this study. Therefore, it was not possible for us to assess the degree of symptoms. To further examine the speculation presented in this study, it is recommended that a systematic interview be conducted prospectively.

Evaluation of the prognostic value of the presence of symptoms in the present study revealed that all asymptomatic patients with OEC and OCCC survived without recurrence, whereas all patients who showed recurrence and died of the disease presented with symptoms. Some studies have reported that prediagnosis high inflammation is associated with decreased ovarian cancer survival, which may be compatible with our results[27,28]. However, as this is a study of some cases, further studies are needed to confirm whether the presence of symptoms is a prognostic factor for OCCC/OEC.

Conclusion

In conclusion, approximately 55% of the patients with early-stage EAOC in this study presented with physical symptoms. The frequency and characteristics of these symptoms varied widely according to the histological type of the tumor, which may reflect the different carcinogenesis mechanisms of OEC, OCCC, and SMBT. Although few studies have focused on understanding the symptoms of ovarian cancer, the importance of patient-reported outcomes has received much attention in recent years, and a proper interview is fundamental to the clinician's work. This study may help to reaffirm the importance of a detailed examination of patients' symptoms to understand their pathophysiology precisely.

Ethics

Ethics Committee Approval: This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (approval number: G531, date: 29.09.2023) and conforms to the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants via an opt-in approach (wherein participants signed a printed informed consent document) or an opt-out approach (wherein participants were informed about the study through the website).

Authorship Contributions

Surgical and Medical Practices: M.O., M.F., K.Y., M.S., S.K., M.T., A.H., K.Y., J.H., M.M., Concept: M.O., K.Y., Design: M.O., K.Y., Data Collection or Processing: M.O., M.F., K.Y., Analysis or Interpretation: M.O., M.F., K.Y., Literature Search: M.O., M.F., K.Y., Writing: M.O., K.Y.

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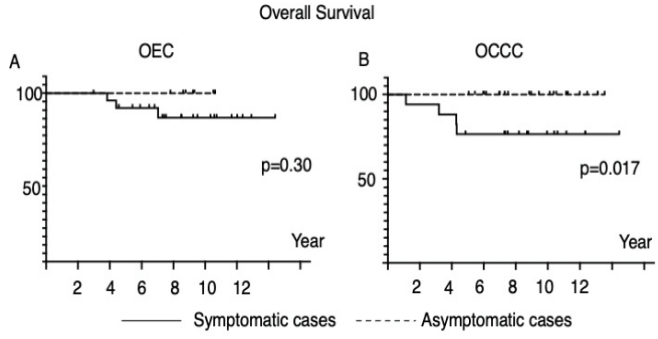
Supplementary Table 1. Comparison of clinical and pathological findings among different symptoms in OEC

	Bleeding	Abdominal disconfort/pain	Symptom (-)	p-value
	n=9	n=15	n=7	
WBC (x10^3/uL)	7.9 (5.60-10.4)	6.3 (5.6-10.7)	5.00 (3.30-8.50)	0.10
N/L ratio	4.6 (2.5-7.7)	4.7 (1.9-8.0)	1.7 (1.0-6.5)	0.094
CA125 (log-scale)	9.0 (5.1-10.0)	8.1 (4.8-9.7)	5.8 (3.6-7.0)	0.023
Size (cm)	12.0 (10.0-15.0)	8.0 (7.0-13.0)	6.4 (4.5-16.5)	0.061
Neoplasm in endometrium	4	5	1	0.44
Capsuled group	6	10	6	
Un-capsuled group	3	5	1	0.62

As for continuous variables, median and interquartile range were described.
As for categorical variables, number was described.
OEC: Ovarian endometrioid carcinoma, WBC: White blood cell, N/L: Neutrophil/lymphocyte



C

Case	Symptom	pStage
1	Bleeding	IC3
2	Bleeding	IC3
3	Pain	IC3

D

Case	Symptom	pStage
1	Discomfort	IC2
2	Discomfort	IC2
3	Discomfort	IA
4	Bleeding	IIIA1(i)

Supplementary Figure 1. Analysis of overall survival from the viewpoint of presence of symptoms

A. Differences in survival based on presence of symptoms in OEC

B. Differences in survival based on presence of symptoms in OCCC

C. Cases of died of disease in OEC were listed. Their symptoms and FIGO stage are as shown

D. Cases of died of disease in OCCC were listed. Their symptoms and FIGO stage are as shown

OEC: Ovarian endometrioid carcinoma, OCCC: Ovarian clear cell carcinoma, SMBT: Seromucinous borderline tumor, FIGO: Federation of Gynecology and Obstetrics