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Full length article

## Atypical endometriosis is related to a higher recurrence rate

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### ABSTRACT

**Objectives:** The aims of this study were to evaluate the clinical characteristics and recurrence rate of atypical endometriosis (AE)<sup>1</sup> compared to typical endometriosis (TE) in addition to the malignant transformation rate among a large cohort.

**Study design:** The medical records of 2681 patients who had undergone surgical treatment of ovarian endometrioma between January 2008 and September 2019 were retrospectively reviewed. The patients were divided into AE (n = 86) and TE (n = 2595) groups. Patients' characteristics and recurrence rates were evaluated and compared between the two groups.

**Results:** The mean size of ovarian cysts was significantly larger in the AE group ( $7.6 \pm 3.5$  cm vs  $6.7 \pm 3.3$  cm,  $p = 0.01$ ) and the proportion of nulliparous women was significantly lower in AE group (65.1 % vs 77.8 %,  $p = 0.008$ ). Otherwise, there were no statistically significant differences in patient characteristics between the two groups. After Cox regression analyses with IPTW was adjusted, the risk factors for recurrent endometrioma were higher preoperative CA125 level  $>48$  U/mL (hazard ratio [HR] = 2.741; 95 % confidence interval [CI] = 1.517–4.952;  $p < 0.001$ ), multilocular cyst (HR = 1.909; 95 % CI = 1.128–3.230;  $p = 0.016$ ), and atypical endometriosis (HR = 2.666; 95 % CI = 1.659–4.284;  $p < 0.001$ ). The AE group displayed a significantly higher cumulative recurrence rate than the TE group ( $p = 0.0057$ , log-rank test). No patients were diagnosed with atypical endometriosis to malignant transformation during the follow-up periods. However, two typical endometriosis patients experienced borderline malignancy and serous carcinoma, respectively.

**Conclusion:** Recurrence rates for AE were higher than for TE. Although the AE group included no patient with malignant transformation in this study, considering the higher recurrence as well as the possibility of malignant transformation, long-term close surveillance is warranted.

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### Introduction

Endometriosis is a benign estrogen-dependent gynecologic disease that occurs mainly among women of reproductive age, and the prevalence rate is estimated to be 5–10 % [1,2]. A defining feature of endometriosis is the presence of endometrial gland and/or stroma outside the uterine cavity, generally on the pelvic

peritoneum and ovaries [3]. Taniguchi et al. reported that approximately 1% of endometriosis cases undergo malignant transformation [4]. In addition, Wilbur et al. reported that women with endometriosis have a two- to three-fold increase in the absolute risk of developing epithelial ovarian cancer [5]. Among the histologic types of ovarian endometriosis, atypical endometriosis (AE) is known to be a precursor lesion of endometriosis-associated ovarian cancer (EAOC) characterized by cytologic atypia and architectural atypia or hyperplasia [6]. "Cytologic atypia" describes the presence of nuclear atypia within the epithelial lining of endometriotic cysts, whereas 'architectural atypia or hyperplasia' refers to the same spectrum of hyperplasia discovered in the endometrium [7]. Tanase et al. emphasized the importance of considering the possibility of malignant change, and strongly recommended carefully following patients in cases when AE is observed [8]. Because of the risk of malignant transformation,

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<sup>1</sup> AE: Atypical endometriosis, ASRM: American Society of Reproductive Medicine, EAOC: Endometriosis-associated ovarian cancer, RR: Relative risk, TE: Typical endometriosis.

most studies regarding atypical endometriosis focused on EAOC. However, other data, such as clinical characteristics, risk factors, and recurrence of AE are limited. Therefore, the aims of this study were to evaluate the clinical characteristics and recurrence rates of AE compared to typical endometriosis (TE) in addition to the malignant transformation rate of AE.

## Materials and methods

A retrospective cohort study was performed in a single gynecological surgery center using data collected between January 2008 and September 2019. During the study period, a total of 3957 patients were surgically treated and displayed pathologically confirmed ovarian endometriosis. Patients were excluded if they had (1) gynecologic malignancy in addition to ovarian endometriosis ( $n = 87$ ) and underwent bilateral oophorectomy ( $n = 17$ ), (2) menopause ( $n = 15$ ), (3) revised American Society of Reproductive Medicine (rASRM) stage of I or II ( $n = 18$ ) at initial surgery [9], or (4) follow-up duration of <6 months ( $n = 1109$ ). The definition of atypical endometriosis included cytologic atypia, architectural atypia, or hyperplasia. According to McCluggage, reactive change of ovarian endometrioma can occur secondary to repeated episodes of hemorrhage and may be confused with atypical endometriosis [10]. Therefore, we excluded those patients who were also diagnosed with cytological atypia or hyperplasia associated with reactive change ( $n = 30$ ). Thus, a total of 2681 patients were included and their data analyzed in the current study. The recurrence of endometrioma was considered when transvaginal or transrectal sonography indicated the presence of a round-shaped cystic mass with a minimum diameter of 20 mm, thick walls, regular margins, homogenous low echogenic fluid content with scattered internal echoes, and the absence of papillary proliferation [11]. If a patient had two endometriomas that were <20 mm and the sum of their diameters was >20 mm, the patient was considered to have endometrioma recurrence. Reoperations were performed when (1) the size of endometrioma was more than 5 cm despite medical treatments, (2) the size of endometrioma was more than 5 cm and medical treatment was unavailable, (3) malignancy was suspected in the recurred cyst, or (4) a procedure was needed for cesarean section or co-existing gynecologic diseases such as myoma or dermoid cyst. In cases of reoperation during the study period, the initial surgery was analyzed. However, if the pathologic results indicated AE in a later surgery, the later surgery was analyzed in the AE group. The study protocol was approved by the Institutional Review Boards and ethics committee of CHA Gangnam Medical Center on the Use of Human Subjects in Research (GCI-20–04); informed consent requirements for the study were waived given its retrospective nature.

Statistical analyses were performed using SPSS 22.0 (IBM, Armonk, NY, USA) and R for Windows, ver. 4.0.2. Chi-square and Fisher's exact tests were used for the analysis of categorical variables. Quantitative variables were compared using the Mann-Whitney  $U$  test. The Kaplan-Meier method was required for calculation of the cumulative probability of recurrence, and the comparison between the curves was performed using the long-rank test.  $P$ -values <0.05 were considered statistically significant. In addition, the inverse probability of treatment weighting (IPTW) method based on the propensity score was used to reduce the effect of selection/allocation bias between the with recurrence and without recurrence groups.

## Results

A total of 2681 patients were included in this study. The median follow-up duration was 26.0 months (range, 6–138 months). Baseline characteristics of the patients are shown in Table 1. The

**Table 1**  
Baseline characteristics of patients.

Clinical characteristics	Patients (n = 2681)
Age (years)	33.2 ± 6.7 (32.0, 16–64)
Parity	
No	2074 (77.4 %)
Yes	607 (22.6 %)
BMI (kg/m <sup>2</sup> )	21.1 ± 3.0 (20.5, 14.7–37.9)
Size of ovarian cyst(s) (cm)	6.7 ± 3.4 (6.0, 0.5–36.4)
Duration of follow-up (months)	36.7 ± 29.2 (26.0, 6–138)
Preoperative CA125 (n = 2358)	81.1 ± 167.0 (48.0, 1.0–5203)
Preoperative AMH (n = 1117)	3.40 ± 2.99 (2.62, 0.01–21.14)
Previous history of endometrioma operation	
No	2449 (91.3 %)
Yes	232 (8.7 %)
Preoperative symptoms	
Pain	1645 (61.4 %)
Bleeding	158 (5.9 %)
Compression symptom	34 (1.3 %)
Infertility	72 (2.7 %)
Growing ovarian cyst	186 (6.9 %)
Incidentally detected	586 (21.9 %)
Laterality	
Unilateral	1931 (72.0 %)
Bilateral	750 (28.0 %)
Cyst nature	
Unilocular	1613 (60.2 %)
Multilocular	1068 (39.8 %)
Cul-de-sac obliteration	
None	922 (34.4 %)
Partial	728 (27.2 %)
Complete	1031 (38.5 %)
ASRM stage	
Stage III	1369 (51.1 %)
Stage IV	1312 (48.9 %)
Medication duration	
None	468 (17.5 %)
<6Mo	323 (12.0 %)
≥6-<12Mo	653 (24.4 %)
≥12Mo-<24Mo	650 (24.2 %)
≥24Mo	587 (21.9 %)
Duration of hormonal treatment (months)	16.1 ± 18.9 (9.0, 0–126)
Atypical endometriosis	
No	2595 (96.8 %)
Yes	86 (3.2 %)
Subsequent pregnancy	
No plan to pregnancy	1755 (65.5 %)
No pregnancy	425 (15.9 %)
Confirmed pregnancy	501 (18.7 %)
Recurrence after previous operation	362 (13.5 %)
Time to recurrence (months) (n = 362)	32.8 ± 26.8 (26, 1–126)
Reoperation after recurrence	66 (18.2 % of recurrent cases/ 2.5 % of total)

Data presented with mean ± standard deviation (median, range) or number (%). BMI, Body mass index; CA125, cancer antigen 125; AMH, anti-Mullerian hormone; ASRM, American society of reproductive medicine.

mean age was 33.2 ± 6.7 years and 77.4 % of the patients were nulliparous. The median duration of postoperative hormonal treatments was 9.0 months (range, 0–126 months). Of the 2681 patients, 86 (3.2 %) were pathologically diagnosed with atypical endometriosis. A total of 362 (13.5 %) patients experienced recurrent ovarian endometrioma with 32.8 ± 26.8 months of mean time to recurrence. Among the 362 patients, 66 (18.2 %) underwent reoperation.

Baseline characteristics of the two groups (TE and AE) are shown in Table 2. The mean size of ovarian cysts was significantly smaller in the TE than the AE group (6.7 ± 3.3 vs. 7.6 ± 3.5 cm,  $p = 0.01$ ) and the proportion of nulliparous women was significantly higher in the TE group than the AE group (77.8 % vs. 65.1 %,  $p = 0.008$ ). Otherwise, there were no statistically significant differences between the two groups.

**Table 2**  
Baseline characteristics of two groups.

Characteristics	Typical endometriosis (TE) (n = 2595)	Atypical endometriosis (AE) (n = 86)	p-value
Age (years) <sup>1</sup>	33.2 ± 6.7 (32.0, 16–64)	34.3 ± 6.3 (33.0, 16–49)	0.083
Parity <sup>2</sup>			0.008
No	2018 (77.8 %)	56 (65.1 %)	
Yes	577 (22.2 %)	30 (34.9 %)	
BMI (kg/m <sup>2</sup> ) <sup>1</sup>	21.1 ± 3.0 (20.6, 14.7–37.9)	21.2 ± 3.2(20.3,15.1–28.9)	0.860
Size of ovarian cyst(s) (cm) <sup>1</sup>	6.7 ± 3.3 (6.0, 0.5–36.4)	7.6 ± 3.5 (6.7, 2.0–23.6)	0.010
Duration of follow-up (months) <sup>1</sup>	36.8 ± 29.3 (26.0, 6–138)	34.2 ± 26.5 (24.0, 6–106)	0.530
Preoperative CA125 (n = 2358) <sup>1</sup>	80.7 ± 165.9 (48.0, 1.0–5203)(n = 2277)	91.1 ± 196.4 (52.5, 3.6–1704)(n = 81)	0.895
Preoperative AMH (n = 1117) <sup>1</sup>	3.40 ± 2.99 (2.62, 0.01–21.14) (n = 1070)	3.52 ± 3.15 (2.81,0.11–10.38) (n = 47)	0.913
Previous history of endometrioma operation <sup>2</sup>			0.327
No	2373 (91.4 %)	76 (88.4 %)	
Yes	222 (8.6 %)	10 (11.6 %)	
Preoperative symptoms <sup>3</sup>			0.672
Pain	1590 (61.3 %)	55 (64.0 %)	
Bleeding	154 (5.9 %)	4 (4.7 %)	
Compression symptom	32 (1.2 %)	2 (2.3 %)	
Infertility	68 (2.6 %)	4 (4.7 %)	
Growing ovarian cyst	180 (6.9 %)	6 (7.0 %)	
Incidentally detected	571 (22.0 %)	15 (17.4 %)	
Laterality <sup>2</sup>			0.224
Unilateral	1874 (72.2 %)	57 (66.3 %)	
Bilateral	721 (27.8 %)	29 (33.7 %)	
Cyst nature <sup>2</sup>			0.655
Unilocular	1559 (60.1 %)	54 (62.8 %)	
Multilocular	1036 (39.9 %)	32 (37.2 %)	
Cul-De-Sac obliteration <sup>3</sup>			0.169
None	896 (34.5 %)	26 (30.2 %)	
Partial	697 (26.9 %)	31 (36.0 %)	
Complete	1002 (38.6 %)	29 (33.7 %)	
ASRM stage <sup>2</sup>			0.827
Stage III	1324 (51.0 %)	45 (52.3 %)	
Stage IV	1271 (49.0 %)	41 (47.7 %)	
Medication duration <sup>3</sup>			0.949
None	451 (17.4 %)	17 (19.8 %)	
<6Mo	312 (12.0 %)	11 (12.8 %)	
≥6–<12Mo	632 (24.4 %)	21 (24.4 %)	
≥12Mo–<24Mo	632 (24.4 %)	18 (20.9 %)	
≥24Mo	568 (21.9 %)	19 (22.1 %)	
Duration of hormonal treatment (months) <sup>1</sup>	16.2 ± 18.9 (9.0, 0–126)	14.3 ± 17.5 (7.5, 0–106)	0.468
Subsequent pregnancy <sup>3</sup>			0.235
No plan to pregnancy	1695 (65.3 %)	60 (69.8 %)	
No pregnancy	417 (16.1 %)	8 (9.3 %)	
Confirmed pregnancy	483 (18.6 %)	18 (20.9 %)	
Time to recurrence (months) (n = 362) <sup>1</sup>	33.1 ± 26.9 (27, 1–126)(n = 344)	26.8 ± 24.9 (18, 6–94)(n = 18)	0.347

Data presented with mean ± standard deviation (median, range) or number (%).

BMI, Body mass index; CA125, cancer antigen 125; AMH, anti-Mullerian hormone; ASRM, American society of reproductive medicine.

<sup>1</sup> Mann-Whitney U test.

<sup>2</sup> Fisher's exact tests.

<sup>3</sup> Chi-square test.

The possible risk factors for recurrent endometrioma are presented in Table 3. There were significant differences between the without and with recurrence groups with respect to age, BMI, size of ovarian cysts, duration of follow-up, preoperative CA125 levels, previous history of endometrioma operation, laterality, surgical method, cyst nature, CDS obliteration, rASRM stage, duration of hormonal treatment, and subsequent pregnancy. The factor of atypical endometriosis showed marginal significance ( $p = 0.052$ ).

Results of the univariate and multivariate analyses for independent risk factors of recurrent ovarian endometrioma, including atypical endometriosis, using the Cox regression method are listed in Table 4. In the univariate analysis, size of ovarian cysts >6 cm (hazard ratio [HR] = 1.418; 95 % confidence interval [CI] = 1.150–1.749;  $p = 0.001$ ), preoperative CA125 level >48.0 U/mL (HR = 1.694; 95 % CI = 1.353–2.122;  $p < 0.001$ ), previous history of endometrioma operation (HR = 1.542; 95 % CI = 1.132–2.102);  $p = 0.006$ ), bilateral endometrioma (HR = 1.397; 95 % CI = 1.124–1.736;  $p = 0.003$ ), multilocular cyst (HR = 1.392; 95 %

CI = 1.131–1.711;  $p = 0.002$ ), atypical endometriosis (HR = 1.927; 95 % CI = 1.199–3.096;  $p = 0.007$ ), CDS obliteration (HR = 1.597; 95 % CI = 1.254–2.035;  $p < 0.001$ ), rASRM stage IV (HR = 1.553; 95 % CI = 1.258–1.917;  $p < 0.001$ ), and duration of medication >9 months (HR = 0.811; 95 % CI = 0.659–0.997;  $p = 0.047$ ) were significant. Factors with  $p$ -values  $\leq 0.20$  in univariate analyses were included in the multivariate Cox regression analysis. In the multivariate analysis, preoperative CA125 level >48.0U/mL (HR = 1.485; 95 % CI = 1.176–1.876;  $p = 0.001$ ), multilocular cyst (HR = 1.270; 95 % CI = 1.011–1.596;  $p = 0.040$ ), atypical endometriosis (HR = 1.771; 95 % CI = 1.050–2.988);  $p = 0.032$ ), CDS obliteration (HR = 1.474; 95 % CI = 1.073–2.025;  $p = 0.017$ ), postoperative medication (HR = 1.749, 95 % CI = 1.226–2.496;  $p = 0.002$ ), and duration of medication >9 months (HR = 0.592; 95 % CI = 0.463–0.756;  $p < 0.001$ ) were statistical significant.

To reduce the effect of selection/allocation bias, inverse probability of treatment weighting (IPTW)-adjusted multivariate Cox regression analyses were performed (Table 5). After adjusting for IPTW, the three dependent risk factors for recurrent ovarian

**Table 3**

Analysis of possible risk factors for recurrent ovarian endometriosis (n = 2681).

Characteristics	No recurrence (n = 2319)	Recurrence (n = 362)	p-value
Age (years) <sup>1</sup>	33.4 ± 6.8 (33, 16–64)	32.1 ± 5.9 (32, 16–48)	0.003
Parity <sup>2</sup>			0.251
No	1785 (77.0 %)	289 (79.8 %)	
Yes	534 (23 %)	73 (20.2 %)	
BMI (kg/m <sup>2</sup> ) <sup>1</sup>	21.1 ± 3.0 (20.6, 14.7–37.9)	20.8 ± 3.0 (20.2, 16.3–34.4)	0.008
Size of ovarian cyst(s) (cm) <sup>1</sup>	6.6 ± 3.2 (6.0, 0.5–36.4)	7.8 ± 3.9 (6.8, 0.8–23.6)	<0.001
Duration of follow-up (months) <sup>1</sup>	33.7 ± 27.5 (23, 6–138)	56.1 ± 32.3 (51, 6–133)	<0.001
Preoperative CA125 (U/mL) (n = 2358) <sup>1</sup>	78.9 ± 172.1 (46.4, 1.0–5203) (n = 2038)	95.2 ± 129.8 (60.7, 8.4–1718) (n = 320)	<0.001
Preoperative AMH (ng/mL) (n = 1117) <sup>1</sup>	3.39 ± 3.01 (2.6, 0.01–21.14) (n = 1011)	3.53 ± 2.84 (2.92, 0.06–13.14) (n = 106)	0.374
Previous history of endometrioma operation <sup>2</sup>			0.005
No	2133 (92.0 %)	316 (87.3 %)	
Yes	186 (8.0 %)	46 (12.7 %)	
Preoperative symptoms <sup>3</sup>			0.353
Pain	1410 (60.8 %)	235 (64.9 %)	
Bleeding	141 (6.1 %)	17 (4.7 %)	
Compression symptom	28 (1.2 %)	6 (1.6 %)	
Infertility	67 (2.9 %)	5 (1.4 %)	
Growing ovarian cyst	164 (7.1 %)	22 (6.1 %)	
Incidentally detected	509 (21.9 %)	77 (21.3 %)	
Laterality <sup>2</sup>			0.008
Unilateral	1692 (73.0 %)	239 (66.0 %)	
Bilateral	627 (27.0 %)	123 (34.0 %)	
Extent of surgery: ovary <sup>2</sup>			0.727
Cyst enucleation only	2175 (93.8 %)	338 (93.4 %)	
One oophorectomy	144 (6.2 %)	24 (6.6 %)	
Extent of surgery: uterus <sup>2</sup>			0.473
Uterus preservation	2179 (94.0 %)	344 (95.0 %)	
Hysterectomy	140 (6.0 %)	18 (0.5 %)	
Extent of surgery: tube <sup>3</sup>			0.402
No	2032 (87.6 %)	325 (89.8 %)	
One tube	159 (6.9 %)	23 (6.3 %)	
Both tube	127 (5.5 %)	14 (3.9 %)	
Surgical method <sup>2</sup>			<0.001
Explo-laparotomy	107 (4.6 %)	37 (10.2 %)	
Laparoscopy or Robotic	2212 (95.4 %)	325 (89.8 %)	
Cyst nature <sup>2</sup>			0.009
Unilocular	1418 (61.1 %)	195 (53.9 %)	
Multilocular	901 (38.9 %)	167 (46.1 %)	
Typical vs. atypical <sup>2</sup>			0.052
Typical	2251 (97.1 %)	344 (95.0 %)	
Atypical	68 (2.9 %)	18 (5.0 %)	
Cul-De-Sac obliteration <sup>3</sup>			<0.001
None	836 (36.0 %)	86 (23.7 %)	
Partial	626 (27.0 %)	102 (28.2 %)	
Complete	857 (37.0 %)	174 (48.1 %)	
rASRM stage <sup>2</sup>			<0.001
Stage III	1225 (52.8 %)	144 (39.8 %)	
Stage IV	1094 (47.2 %)	218 (60.2 %)	
Medication duration <sup>3</sup>			<0.001
None	417 (18.0 %)	51 (14.1 %)	
<6 Mo	271 (11.7 %)	52 (14.4 %)	
≥6-<12 Mo	571 (24.6 %)	82 (22.6 %)	
≥12 Mo-<24 Mo	583 (25.1 %)	67 (18.5 %)	
≥24 Mo	477 (20.6 %)	110 (30.4 %)	
Duration of hormonal treatment (months) <sup>1</sup>	15.6 ± 18.3 (9.0, 0–126)	19.4 ± 22.3 (11.0, 0–124)	0.019
Subsequent pregnancy <sup>3</sup>			0.01
No plan to pregnancy	1542 (66.5 %)	213 (58.8 %)	
No pregnancy	351 (15.1 %)	74 (20.5 %)	
Confirmed pregnancy	426 (18.4 %)	75 (20.7 %)	

Data are presented as mean ± standard deviation (median, range) or number (%).

BMI, body mass index; CA125, cancer antigen 125; AMH, anti-Mullerian hormone; rASRM, revised American Society of Reproductive Medicine.

<sup>1</sup> Mann-Whitney *U* test.<sup>2</sup> Fisher's exact tests.<sup>3</sup> Chi-square test.

endometrioma were preoperative CA125 level >48.0 U/mL (HR = 2.741; 95 % CI = 1.517–4.952; *p* < 0.001), multilocular cyst (HR = 1.909; 95 % CI = 1.128–3.230; *p* = 0.016), atypical endometriosis (HR = 2.666; 95 % CI = 1.659–4.284; *p* < 0.001).

The cumulative recurrence rates by Kaplan-Meier analysis at 12, 24, 36, and 60 months were 4.4 %, 8.3 %, 12.0 %, and 21.3 %, respectively (Fig. 1). The AE group had a significantly higher

cumulative recurrence rate than the TE group according to the log-rank test (*p* = 0.0057) in the original cohort (Fig. 2A), and after adjusting with IPTW, the AE group showed a significantly higher cumulative recurrence rate (*p* = 0.003). (Fig. 2B)

No patients were diagnosed with atypical endometriosis to malignant transformation during the follow-up period. However, two typical endometriosis patients experienced recurrent disease

**Table 4**

Univariate and multivariate analyses for independent risk factors of recurrent ovarian endometrioma using the Cox regression method.

Characteristics	Univariate		Multivariate	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Risk factors of recurrence				
Age >32 years (vs. ≤ 32 years)	0.913 (0.742–1.123)	0.390		
BMI >20.5 kg/m <sup>2</sup> (vs. ≤20.5)	0.926 (0.752–1.139)	0.466		
Size of ovarian cysts >6.0 cm (vs. ≤ 6.0)	1.418 (1.150–1.749)	0.001	1.083 (0.828–1.417)	0.561
Preoperative CA125 level >48.0 U/mL (vs. ≤ 48.0) (n = 2358)	1.694 (1.353–2.122)	<0.001	1.485 (1.176–1.876)	0.001
Previous history of endometrioma operation (vs. no)	1.542 (1.132–2.102)	0.006	1.201 (0.844–1.708)	0.308
Bilateral (vs. unilateral)	1.397 (1.124–1.736)	0.003	1.105 (0.813–1.501)	0.525
Explo-laparotomy (vs. laparoscopic or robotic)	0.725 (0.514–1.022)	0.067	0.889 (0.578–1.368)	0.593
Multilocular cyst (vs. unilocular)	1.392 (1.131–1.711)	0.002	1.270 (1.011–1.596)	0.040
Atypical endometriosis (vs. typical)	1.927 (1.199–3.096)	0.007	1.771 (1.050–2.988)	0.032
CDS obliteration (vs. no obliteration)	1.597 (1.254–2.035)	<0.001	1.474 (1.073–2.025)	0.017
rASRM stage IV (vs. III)	1.553 (1.258–1.917)	<0.001	1.069 (0.782–1.461)	0.675
Postoperative medication (vs. no)	1.345 (0.999–1.810)	0.051	1.749 (1.226–2.496)	0.002
Duration of medication >9 months	0.811 (0.659–0.997)	0.047	0.592 (0.463–0.756)	<0.001
Subsequent pregnancy (vs. no)	0.861 (0.667–1.111)	0.249		

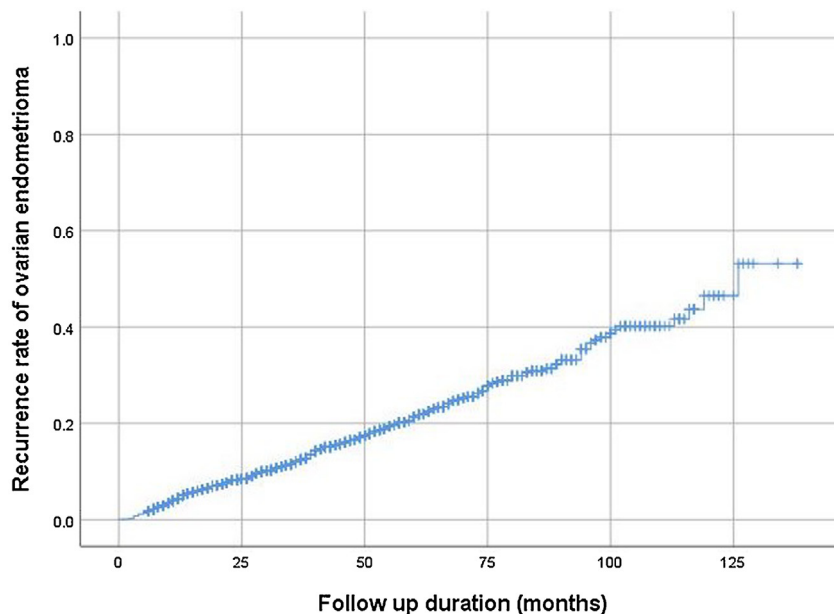
HR, hazard ratio; CI, confidence interval; BMI, body mass index; CA125, cancer antigen 125; rASRM, revised American Society for Reproductive Medicine; CDS, cul-de-sac; d/t, due to; endo, endometriosis; Mo, month.

**Table 5**

Multivariate analysis of independent risk factors of recurrent ovarian endometrioma using the Cox regression method adjusted with inverse probability of treatment weighting (IPTW).

Characteristics	Multivariate analysis (non-adjusted with IPTW)		Multivariate adjusted with IPTW	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Risk factors of recurrence				
Preoperative CA125 level >48.0 U/mL (vs. ≤ 48.0) (n = 2358)	1.485 (1.176–1.876)	0.001	2.741 (1.517–4.952)	<0.001
Multilocular cyst (vs. unilocular)	1.270 (1.011–1.596)	0.040	1.909 (1.128–3.230)	0.016
Atypical endometriosis (vs. typical)	1.771 (1.050–2.988)	0.032	2.666 (1.659–4.284)	<0.001
CDS obliteration (vs. no obliteration)	1.474 (1.073–2.025)	0.017	0.854 (0.394–1.855)	0.691
Postoperative medication (vs. no)	1.749 (1.226–2.496)	0.002	1.711 (0.694–4.215)	0.243
Duration of medication >9 months	0.592 (0.463–0.756)	<0.001	0.890 (0.460–1.721)	0.729

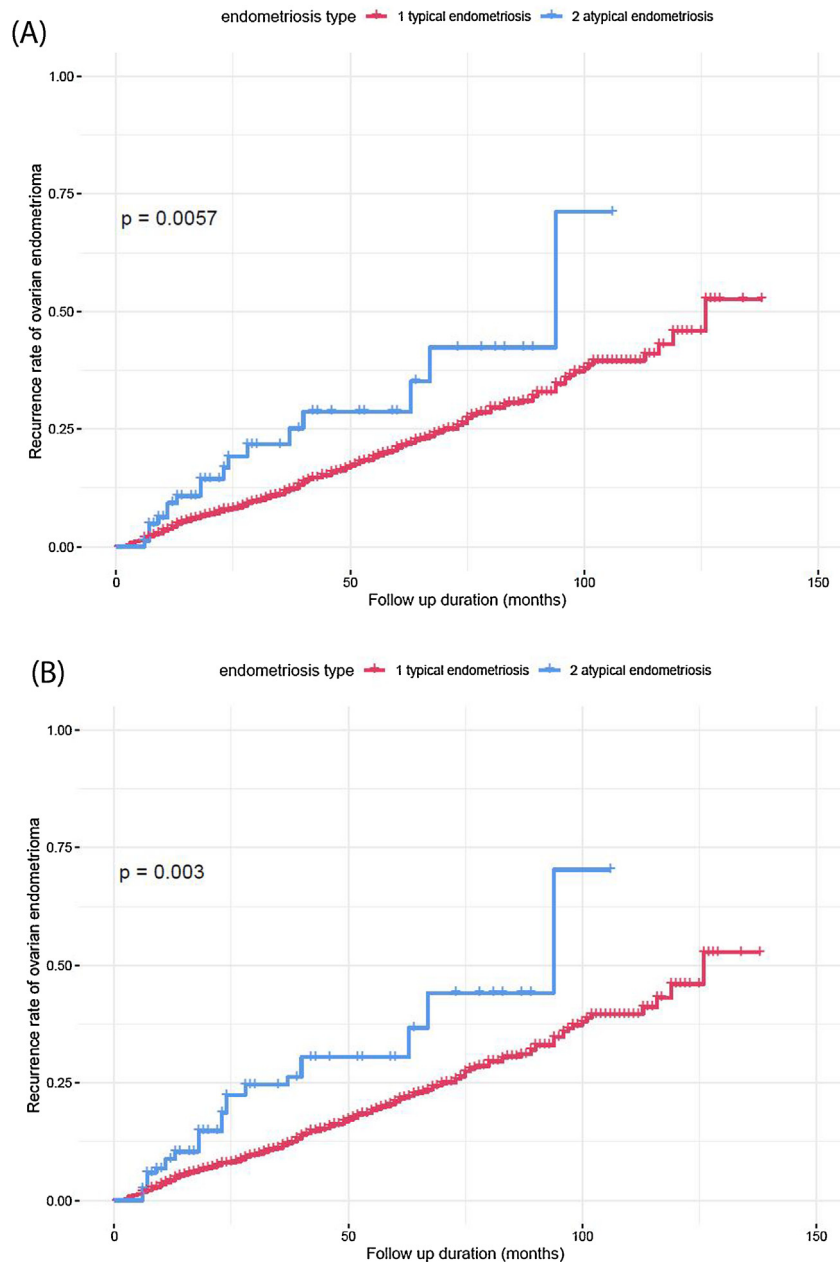
HR, hazard ratio; CI, confidence interval; BMI, body mass index; CA125, cancer antigen 125; rASRM, revised American Society for Reproductive Medicine; CDS, cul-de-sac; d/t, due to; endo, endometriosis; Mo, month.

**Fig. 1.** Cumulative recurrence rate of ovarian endometrioma using the Kaplan-Meier analysis.

with borderline malignancy and malignant ovarian cancer; one was diagnosed with a seromucinous borderline tumor associated with endometriosis on the same side of the ovary 7 years after initial surgery, and the other was diagnosed with ovarian serous carcinoma on the opposite side after 33 months.

## Discussion

The main finding of this study was that the AE group displayed higher recurrence in addition to the clinical characteristics of larger cyst size and higher proportion of multiparity



**Fig. 2.** Comparison of cumulative recurrence rate of typical and atypical endometriosis (log-rank test) in the original cohort (A) and IPTW-adjusted cohort (log-rank test) (B).

than the TE group. During the  $32.4 \pm 26.5$  months follow-up period, no patient was diagnosed with atypical endometriosis to malignant transformation. To the best of our knowledge, this is the first large cohort study to evaluate the recurrence rates of atypical endometriosis.

Although it has been overlooked due to the more important issue of malignant transformation in atypical endometriosis, one of the important aspects of endometriosis is a high rate of recurrence. However, there is no published study on atypical endometriosis as a risk factor for recurrence. The mechanisms explaining recurrence are not clear. The hypothesis that explains the mechanism of recurrence is that recurrent lesions might originate from remnant lesions or de novo cells resulting from retrograde bleeding after surgery [12]. Our results indicate that AE displays a significantly higher cumulative recurrence rate than TE, along with higher CA125 level and multilocular cysts.

We assumed that the inherent characteristics of AE contribute to the recurrence. There is a biomarker called Ki-67 which is a nuclear protein observed in proliferating cells such as tumors and endometriosis [13–15]. Cells tend to have a more aggressive course with vascular invasion, proliferation, and metastasis if the Ki-67 proliferation rate is high [13]. Ogawa et al. found significantly higher Ki-67 index in AE than in TE but lower than in ovarian cancer [16]. We, therefore, assumed that AE tends to recur more frequently than TE.

As we hypothesized, AE was related to a higher recurrence rate than TE. We think that residual atypical endometriotic lesions that were not removed completely at initial surgery could aggressively proliferate. However, a remaining source of confusion was the difference in the mean size of ovarian cysts. Several studies have demonstrated that larger cyst size is related to higher recurrence [17–19]. In our results, the mean size of ovarian cysts of the AE

group was larger than the TE group. ( $7.6 \pm 3.5$  vs.  $6.7 \pm 3.3$  cm,  $p = 0.01$ ). Although the degree of difference in size between the two groups was very tiny, this difference may lead to more frequent recurrence among patients with AE. Alternatively, it is possible that the tumor-like features of AE can induce increased size in cysts, as well as more frequent recurrence. Further, we observed that there were more parous women among the AE group and the reason for this is unclear. We postulate this may be because the mean age of the AE group was higher, although this age difference was not statistically significant.

Endometriosis is considered a risk factor for ovarian cancer. The possible pathogenesis of the malignant transformation of endometriosis to EAO is considered that cyclic hemorrhage into the endometriotic cyst leads to the accumulation of blood components and can induce inflammation by oxidative stress, which then potentiates DNA damage [20]. Additional molecular alterations were also noted; ARID1A/BAF250a, PIK3CA, CTNNB1 and PTEN mutation, microsatellite instability, and loss of heterozygosity [21–25]. According to the meta-analysis by Wentzensen et al., relative risk (RR) of all invasive ovarian cancers along with endometriosis was 1.35 (95 % confidence interval (CI), 1.07–1.71), RR of endometrioid carcinoma was 2.32 (CI, 1.36–3.95), and clear cell carcinoma was 2.87 (CI, 1.53–5.39) [26]. Thomsen et al. reported in a systematic review of the risk factors for the development of EAO among patients with endometriosis [27]. In their review, the risk factors included older age at the time of diagnosis, solid component, postmenopausal status, larger size ( $\geq 9$  cm) of endometrioma, nulliparity, and hyperestrogenism [27]. In our study, atypical endometriosis was associated with a larger cyst size. However, parity displayed a different pattern; atypical endometriosis related to a higher rate of multiparity.

Atypical endometriosis is considered a premalignant lesion of the subtype of endometrioid and clear cell carcinoma. This owing to the coexistence of AE and ovarian cancer had been reported several times. However, the cases of AE that transformed to cancer are rarely reported [8,28]. Tanase et al. reported a case of 33-year-old women whose disease progressed from a TE to AE and finally to endometrioid adenocarcinoma over 10 years and three laparoscopic surgeries [8]. Although no case recurred from AE to ovarian cancer in reoperation in our study, it will be helpful for AE patients to be followed up carefully.

As in other retrospective studies, our study has several limitations. First, we did not consider the types of postoperative medications. Although the exact mechanism is not clarified, postoperative medical treatment is known to delay recurrence [29,30]. However, there was no significant difference in the duration of medications between the AE and TE groups. Second, our study included women who conceived after their initial surgery. According to several previous studies, postoperative pregnancy prevents the recurrence of endometriosis [17,31,32]. Although there were no significant differences in the proportion of women who conceived after surgery between AE and TE groups, it may affect results. Third, we defined recurrence as the presence of cysts more than 20 mm in size as identified by ultrasonography, not by histological confirmation, and identification of cysts is therefore dependent upon the skill of the ultrasonography operator, which can vary. Additionally, we did not evaluate the recurrence of pain. In practice, the recurrence of pain is frequent and important regardless of ultrasonography findings. The strength of the present study, meanwhile, is that it is the first large cohort study to analyze the clinical characteristics of AE and its recurrence rate compared to TE, and to reduce the selection bias, we analyzed with the IPTW method.

In conclusion, AE appears to be related to higher recurrence rates compared to TE. Further prospective studies are needed to confirm our findings and close surveillance is needed for patients

with AE, given not only the possibility of malignant change but also of recurrence.

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## Declaration of Competing Interest

The authors report no declarations of interest.

## Acknowledgement

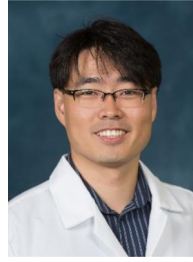
None.

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