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Clinicopathological and prognostic outcomes of endometriosis-associated ovarian cancer

Endometriozisle ilişkili over kanserinin klinikopatolojik ve prognostik sonuçları

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ABSTRACT

Aim: The aim of this study is to investigate the clinicopathological characteristics and prognostic value of endometriosis in patients with ovarian cancer.
Materials and Methods: A retrospective analysis was performed on 273 patients with ovarian carcinoma between January 2013 and December 2023. Patients were stratified into endometriosis-associated ovarian carcinoma (EAOC) and non-endometriosis-associated ovarian carcinoma (non-EAOC). Clinicopathological variables, including age, menopausal status, tumor size and volume, FIGO stage, histological subtype, serum tumor markers, and survival outcomes, were evaluated.
Results: EAOC patients were significantly younger than non-EAOC patients (respectively 51 ± 11.4 years, 59 ± 11.2 years; p = 0.002). EAOC cases were more frequently diagnosed at FIGO stage I than non-EAOC cases (p = 0.001), whereas FIGO stage (III) disease was more prevalent in the non-EAOC group (p = 0.007). No significant differences were observed in CA-125 levels between groups. CA 19-9 levels were elevated in the EAOC group (p = 0.012). Recurrence rates and survival outcomes did not differ significantly between the groups.
Conclusion: EAOC cases were diagnosed at a younger age and presented at an earlier FIGO stage and had elevated CA 19-9 levels. However, survival outcomes did not significantly differ between EAOC and non-EAOC groups.

Keywords: *Endometriosis, Ovarian neoplasms, Endometriosis-associated ovarian cancer, Survival outcome*

ÖZ

Amaç: Bu çalışmanın amacı, over kanseri olan hastalarda endometriozisin klinikopatolojik özelliklerini ve prognostik değerini araştırmaktır.
Gereçler ve Yöntemler: Ocak 2013 ile Aralık 2023 tarihleri arasında over karsinomu tanısı alan 273 hasta retrospektif olarak analiz edildi. Hastalar, endometriozisle ilişkili over karsinomu (EAOC) ve endometriozisle ilişkili olmayan over karsinomu (non-EAOC) olmak üzere iki gruba ayrıldı. Yaş, menopoz durumu, tümör boyutu ve hacmi, FIGO evresi, histolojik alt tip, serum tümör belirteçleri ve sağkalım sonuçları gibi klinikopatolojik değişkenler değerlendirildi.
Bulgular: EAOC hastaları, non-EAOC hastalarına göre anlamlı düzeyde daha gençti (sırasıyla 51 ± 11,4 yıl, 59 ± 11,2 yıl; p = 0,002). EAOC grubunda FIGO evre I'de tanı alma oranı daha yüksekti (p = 0,001), buna karşılık non-EAOC grubunda evre III hastalık daha yaygındı (p = 0,007). Gruplar arasında CA-125 düzeylerinde anlamlı fark saptanmazken, CA 19-9 düzeyleri EAOC grubunda daha yüksekti (p = 0,012). Nüks oranları ve sağkalım sonuçları gruplar arasında anlamlı fark göstermedi.
Sonuç: EAOC hastaları daha genç yaşta ve daha erken FIGO evresinde tanı almakta ve CA 19-9 düzeyleri daha yüksek bulunmaktaydı. Ancak, EAOC ve non-EAOC grupları arasında sağkalım sonuçları açısından anlamlı fark gözlenmedi.

Anahtar Kelimeler: *Endometriozis, Over neoplazileri, Endometriozisle ilişkili over kanseri, Sağkalım sonucu*

INTRODUCTION

Endometriosis, characterized by the presence of endometrial-like tissue in locations outside the uterine cavity, has been associated with the pathogenesis of epithelial ovarian cancer (EOC). This association was first documented by Sampson in 1925, who reported malignant transformation in endometriotic lesions (1). A substantial body of epidemiological evidence consistently demonstrates an elevated ovarian cancer risk in patients with endometriosis, with transformation rates estimated at 1–2.5% and relative risks ranging from 1.3 to 1.9 (2). This association manifests as either malignant progression of endometriosis to invasive carcinoma or the coexistence of both entities, termed endometriosis-associated ovarian cancer (EAOC) (3). Despite refinements to Sampson's criteria, the histopathological classification of EAOC remains contentious (4).

Emerging evidence suggests that EAOC may represent a distinct clinicopathological subset, with patients often presenting at younger ages, earlier FIGO stages, and exhibiting improved survival outcomes compared to non-EAOC (5,6). While some studies have indicated a more favorable prognosis for EAOC compared to non-EAOC, others have not reported a significant survival advantage (7,8). Consequently, this study aimed to investigate the clinicopathological characteristics and prognostic value of endometriosis in patients with ovarian cancer.

MATERIALS AND METHOD

This retrospective study analyzed 273 patients with histologically confirmed EOC treated at a tertiary gynecologic oncology referral center from January 2013 to December 2023. Ethical approval was obtained from the Research Ethics Committee of the hospital (approval number: 2024/010.99/6/2). As this was a retrospective study, patient consent was not a requirement.

Patients were stratified into EAOC and non-EAOC using Sampson-Scott criteria, which require (i) the coexistence of carcinoma and endometriosis within the same ovary, (ii) the presence of similar histological patterns, (iii) exclusion of metastatic neoplasms, and (iv) histopathological evidence of malignant transition (1,4). Patients with concurrent non-EOC malignancies were excluded.

Overall survival (OS) was defined as the interval from histologic diagnosis to all-cause mortality or censoring at the last follow-up. Progression-free survival (PFS) was calculated from diagnosis to radiologic or pathologic recurrence, disease progression per RECIST 1.1 criteria, or censoring (9). Survival data were extracted from institutional records and national death registries. Loss to follow-up was defined as ≥12 months without clinical contact.

Sociodemographic, clinicopathologic variables were abstracted from electronic health records. Pathologic parameters included maximal tumor diameter, laterality (unilateral/bilateral), FIGO stage (2014 criteria), and histologic subtype (10). Clinical variables comprised age at diagnosis, menopausal status, and preoperative serum CA-125 and CA 19-9 (IU/mL) levels.

Statistical Analysis

Statistical analyses were performed using R version 4.2.1 with RStudio. Age, which demonstrated a normal distribution, was compared between the EAOC and non-EAOC using an independent two-sample Student's t-test. Non-normally distributed variables—including maximum tumor diameter, tumor volume, CA-125, and CA 19-9—were analyzed via the Mann-Whitney U test. Categorical variables, including menopausal status, FIGO stage, endometrial pathology, and chemotherapy/radiotherapy status, were analyzed using Pearson's chi-square test. In instances where expected cell counts were below 5, Fisher's exact test was implemented. Survival outcomes were evaluated using Kaplan-Meier curves followed by log-rank tests. The statistical significance was set at $p < 0.05$.

RESULTS

Among 273 ovarian cancer cases, 22 (7.9%) met histopathological criteria for EAOC, with the remaining 251 (92.1%) constituting the non-EAOC. Patients in the EAOC group were significantly younger than those in the non-EAOC group (51 ± 11.4 years vs. 59 ± 11.2 years; $p = 0.002$). While the proportion of premenopausal women was higher in the EAOC group, the difference did not reach statistical significance (40.9% vs. 20.7%; $p = 0.057$).

No significant differences were found between the EAOC and non-EAOC groups in terms of median tumor size (10 cm [IQR: 5–14] vs. 7 cm [IQR: 5–11]; $p = 0.136$) or tumor volume (178 cm^3 [IQR: 46–685] vs. 68 cm^3 [IQR: 16–283]; $p = 0.104$). Preoperative serum CA-125 levels and rates of synchronous endometrial pathology were comparable between groups ($p > 0.05$). CA 19-9 levels were significantly elevated in EAOC (median: 30 U/mL [IQR: 7–204] vs. 9 U/mL [IQR: 4–21]; $p = 0.012$). Unilateral tumor involvement was more frequent in EAOC (68.2% vs. 43.8%; $p = 0.048$), though laterality distribution (left/right/bilateral) did not differ significantly ($p = 0.075$).

EAOC patients were more frequently diagnosed at FIGO stage I (54.5% vs. 20.7%; $p = 0.001$), and whereas FIGO stage III was more prevalent in the non-EAOC group (59.4% vs. 27.3%; $p = 0.007$). Both groups demonstrated similar rates of benign endometrial lesions (EAOC: 90.9% vs. non-EAOC: 92.4%; $p = 0.681$). No significant differences in recurrence ($p = 0.82$) or mortality ($p = 0.76$) were observed (Table 1).

DISCUSSION

The present study indicated that 7.6% of ovarian carcinoma cases were associated with endometriosis, with approximately 70% of EAOC manifesting as either clear cell or endometrioid carcinoma histology, consistent with the findings of Chul Ju et al (11). This incidence rate is lower than the 10% to 18% reported in earlier studies (12,13). The specific mechanisms that lead to the malignant transformation of endometriotic lesions are not yet fully understood. However, a hypothesis has been postulated that, in women of reproductive age, an altered immune response combined with a hormonal environment marked by estrogen

dominance and progesterone deficiency may contribute to the progression from benign endometriosis to malignant disease (14).

A mounting body of evidence indicates that EAOCs are more frequently diagnosed at earlier stages in comparison to non-EAOCs. Wang et al. documented 88.2% of EAOCs as stage I versus 15.8% of non-EAOCs, while Kumar et al. recorded 49% of EAOCs at FIGO stage I/II (5,12). A similar observation was made by Erzen et al., who reported stage I diagnoses in 67% of EAOCs compared to 27.6% of non-EAOCs (13). The findings of this study are consistent with these observations, with 54.5% of EAOCs in the study group presenting as stage I compared to 20.7% of non-EAOCs, thereby further strengthening the association between endometriosis and earlier stage malignancy.

Consistent with established evidence, EAOCs are predominantly diagnosed in younger patients and at earlier disease stages, with lower histological grades compared to non-EAOCs (16–18). A recent cohort study reinforced this pattern, revealing that EAOC patients were, on average, six years younger and 35% more likely to be premenopausal than non-EAOC patients (19). Mangili et al. similarly reported a mean diagnostic age of 55 years for EAOCs versus 62 years for non-EAOCs (20). Mirroring these trends, our cohort demonstrated a significantly younger mean age in the EAOC group (51 years) relative to non-EAOC cases (59 years), underscoring the distinct clinical profile of endometriosis-associated malignancies.

The diagnosis of EAOC relies on invasive laparoscopy with histopathological confirmation. However, the widespread application of this approach is constrained by its high cost and procedural invasiveness, underscoring the need for non-invasive alternatives. While CA125, a biomarker in ovarian cancer surveillance, exhibits high sensitivity, its low specificity and inconsistent ability to distinguish EAOC from benign endometriosis limit its clinical use (21). Most studies, including ours, found no significant differences in CA125 levels between EAOC and non-EAOC cases (22,23), though Wang et al. reported lower CA125 levels in EAOC versus non-EAOC cases (122.9 U/mL vs. 1377.5 U/mL) (5). These discrepancies highlight the need for more reliable biomarkers. Emerging evidence suggests that biomarkers such as CA19-9 show promise (24). Our study observed elevated CA19-9 levels in EAOC. While CA19-9 is not suggested as a diagnostic marker for endometriosis-associated malignancy, elevated levels warrant thorough clinical evaluation to improve risk stratification and guide management.

The extant research on EAOC has largely centered on its clinicopathological and prognostic distinctions from non-EAOC. However, many of these studies have been constrained by limited sample sizes and have yielded inconsistent findings. While some studies suggest EAOC is diagnosed at an earlier stage and confers a more favorable prognosis (25-27), others report no significant differences in clinical outcomes (28-30). Consistent with these findings, our study observed no significant differences in recurrence rates or survival outcomes between EAOC and non-EAOC, though this may be influenced by sample size and follow-up duration.

Table 1. Comparison of clinicopathological characteristics between ovarian cancer patients with and without endometriosis

Variable	With Endometriosis (n=22)	Without Endometriosis (n=251)	p-value
Age (mean ± SD) (years)	51 ± 11.4	59 ± 11.2	0.002
Menopausal Status			
Premenopausal	9 (40.9%)	52 (20.7%)	0.057
Postmenopausal	13 (59.1%)	199 (79.3%)	
Tumor size (cm)	10 (5-14)	7 (5-11)	0.136
Tumor Volume (cm^3)	178 (46-685)	68 (16-283)	0.104
CA 125 (U/mL)	249 (74-1517)	547 (94-1693)	0.262
CA 19-9 (U/mL)	30 (7-204)	9 (4-21)	0.012
Laterality of tumor			
Unilateral	15 (68.2%)	110 (43.8%)	0.048
Bilateral	7 (31.8%)	141 (56.2%)	
Tumor side			
Left Ovary	7 (31.8%)	52 (20.7%)	0.075
Right Ovary	8 (36.4%)	56 (22.3%)	
Both Ovaries	7 (31.8%)	143 (57.0%)	
Tumor Stage			
Stage I	12 (54.5%)	52 (20.7%)	0.001
Stage II	3 (13.6%)	32 (12.7%)	N/A
Stage III	6 (27.3%)	149 (59.4%)	0.007
Stage IV	1 (4.5%)	18 (7.2%)	N/A
Endometrial Pathology			
Benign	20 (90.9%)	232 (92.4%)	0.681
Malignant	2 (9.1%)	19 (7.6%)	
Concurrent Endometrial Pathologies			
Benign	20 (90.9%)	229 (91.2%)	0.706
Endometrioid Carcinoma	1 (4.5)	4 (1.6)	
Atypical Hyperplasia	1 (4.5)	4 (1.6)	
Serous Carcinoma	0 (0)	11 (4.4)	
Clear Cell Carcinoma	0 (0)	1 (0.4)	
Carcinosarcoma	0 (0)	2 (0.8)	
Recurrence	9 (40.9%)	112 (44.6%)	0.911
Mortality	5 (22.7%)	116 (46.2%)	0.057
Chemotherapy	21 (95.5%)	205 (81.7%)	0.140
Radiotherapy	2 (9.1%)	9 (3.6%)	0.219

Future research involving larger, multicenter cohorts and extended follow-up durations is essential to deepen our understanding of the pathophysiology of EAOC, improve diagnostic methods, and explore tailored treatment strategies.

This study presents several limitations inherent to its retrospective design, reliance on single-center data, and the small sample size of patients with EAOC, which consequently may affect the generalizability of the findings. The absence of molecular and genetic analyses further constrains our understanding of the mechanistic pathways underlying the malignant transformation associated with endometriosis. Additionally, the incompleteness of clinical data regarding hormonal therapies is a significant shortcoming. Future investigations should aim to incorporate comprehensive molecular profiling to clarify the pathogenesis of EAOC, identify novel biomarkers for early detection, and assess personalized therapeutic modalities, including targeted therapies and immunotherapies, to enhance clinical outcomes.

CONCLUSION

These findings of the study indicated that patients with EAOC are diagnosed at a younger age and present with an earlier FIGO stage compared to those with non-EAOC. However, survival outcomes did not differ significantly between the groups.

Ethical Approval
Ethical approval for this study was provided by the Research Ethics Committee of the Kartal City Hospital (Approval: 2024/010.99/6/2, 26.07.2024). The database management in accordance with privacy legislation and the presented study in accordance with the ethical principle of the Declaration of Helsinki).

Conflict of Interest
No potential conflict of interest was reported by the author(s).

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Authors' Contributions
All authors attest they meet the International Committee for Medical Journal Editors (ICMJE) criteria for authorship. EK: Conceptualization, Data Curation, Writing – Original Draft, Writing –Review & Editing. SSK: Data Curation, Conceptualization, Writing – Original Draft, Writing – Review & Editing. SS: Formal analysis, Writing – Original Draft, Writing –Review & Editing.

All authors participated in the revision of the manuscript and revised the manuscript critically for important intellectual content. All of the authors have read and approved the final version of this manuscript.

Data Sharing Statement
The dataset used and analyzed in the study is available from the corresponding author upon reasonable request.

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