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Effect of adenomyosis on prognosis of patients with endometrial cancer

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SUMMARY

OBJECTIVE: Our goal was to contrast the prognoses of patients with endometrial cancer who had adenomyosis against those that did not.

METHODS: All patients who had received surgical staging for hysterectomy-based endometrial cancer had their medical data retrospectively examined. The analysis covered 397 patients, who were split into two groups depending on the presence of adenomyosis. Comparisons were made between patients covering type of surgery, histopathology, endometrial cancer stage, lymphovascular space invasion, presence of biochemical or histochemical markers, adjuvant therapy, presence of adenomyosis in the myometrial wall, and outcomes in terms of overall survival and disease-free survival.

RESULTS: There is no statistically significant difference in the 5-year disease-free survival or overall survival rates between endometrial cancer patients with and without adenomyosis. This is based on comparisons of tumor stage, tumor diameter, histological type and grade of tumor, myometrial invasion, lymphovascular space invasion, and biochemical markers that affect the course of the disease. The median follow-up times were 61 months for the adenomyosis-positive group and 56 months for the group without adenomyosis.

CONCLUSION: Coexisting adenomyosis in endometrial cancer has no bearing on survival rates and is not a prognostic factor.

KEYWORDS: Adenomyosis. Endometrium cancer. Gynecology. Prognosis. Survival.

INTRODUCTION

Endometrial cancer (EC) is the sixth most detected cancer and the 14th most prevalent cause of cancer death in women globally[1], affecting 2.8% of women at some point in their lifetime[2]. Patients typically present with uterine-confined pathology and have high survival rates. The key predictors of cancer outcome are histological character, tumor grade and size, age, degree of myometrial invasion, lymph node involvement, and disease stage[3].

One of the most prevalent pathological signs in hysterectomy tissues is ectopic endometriosis (known as adenomyosis), which spreads from the endometrium into the uterus, the myometrium, and the endometrial glands. With a varying prevalence of 12–66%[4], it is one of the most common ancillary histopathological results of EC, especially of the endometrioid histotype.

Numerous studies have investigated whether adenomyosis is present in EC patients. Those that investigated the importance of adenomyosis in endometrial adenocarcinoma suggested that it had negative impacts on EC[5,6]. However, in other studies, adenomyosis with EC has been linked to early-stage malignancy and extended surveillance[7]. Furthermore, subsequent investigations have demonstrated that adenomyosis does not negatively affect the prognosis and questionnaires of EC patients[8,9]. It is therefore still unclear whether EC and adenomyosis are related.

Long-term evaluation of the prognosis and surveillance of patients with EC has focused on the occurrence of adenomyosis in this population. As a result, our goal was to assess how adenomyosis affected the prognosis of women with EC.

METHODS

All women (n=425) operated on for EC between January 2016 and December 2021 had their medical records retrospectively evaluated. We established the inclusion and exclusion criteria to qualify patients for additional investigation. To be included, patients required a preoperative assessment, a thorough medical history record, surgical therapy entailing at least a hysterectomy, and a record of postoperative pathology results. Patients were excluded if they had received preoperative chemotherapy

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or endocrine treatment, had primary tumors in other parts of the body (such as the breast or colon), or if significant data were lacking. The National Ethics Committee gave the Bakırköy Dr. Sadi Konuk Training and Research Hospital in Istanbul permission to conduct this study (No. 2020-01-07, Bakırköy Dr. Sadi Konuk Training and Research Hospital).

The pathological reports from the chosen patients (n=397) were thoroughly examined for EC. We excluded 28 individuals, 12 of whom had previously undergone chemotherapy and surgery for breast cancer, and 16 of whom had already undergone chemotherapy and surgery for colon cancer.

All patients had had hysterectomy procedures, either with or without pelvic/paraaortic lymphadenectomy and pelvic wash cytological analysis. They all had been closely monitored, received treatment, had radiotherapy or chemotherapy combined with radiotherapy according to their stages, and received follow-ups every 6 months if deemed necessary following the multidisciplinary team conference. Once the clinical presentations and prognoses of the two concurrent disorders were understood, the clinicopathological traits and oncological outcomes were assessed. The data variables considered included age, menopausal status, tumor grade, stage, preoperative cancer antigen CA-125 level, and adenomyosis status. Tumor stage and histological grade were established in accordance with the National Comprehensive Cancer Network guidelines[10]. Our primary conclusion is that the prognostic factors used are poor. These include tumor stage, histological type and grade, lymphovascular space invasion, myometrial invasion, age and tumor diameter, biochemical and histochemical markers, and overall survival (OAS) and disease-free survival (DFS) rates.

High (II–III) and low (I) histological grades were distinguished. From hospital records, patient information was also gathered, including age, body mass index (BMI), gravity, nulliparity, medical comorbidities, operation type, adjuvant treatment (chemotherapy and/or radiotherapy), follow-up, and relapse. Patients were divided into two groups based on the presence or absence of adenomyotic tissue. Women in group A had adenomyosis in addition to EC, and those in group B had EC only. The data related to the two groups were statistically compared.

The SPSS statistics software for Windows version 21.0 (IBM Corp., Armonk, NY) was utilized for the statistical analysis. The W2 test was used to compare categorical data, the Kaplan–Meier tests were used to compute OAS and DFS, and the log-rank test was used to compare the results. For OAS, Cox proportional hazards regression models were run with single and multiple covariates and a 95% confidence interval (CI). Statistics were found to be significant at $p<0.05$.

RESULTS

The demographic data, surgical procedures, and outcomes are evaluated in Table 1. The comparisons in Table 1 include age (p:0.342), BMI (p:0.257), gravity (p:0.947), nulliparity (p:0.448), menopausal status (p:0.757), surgical method (laparoscopy vs. laparotomy) (p:0.279), degree of pelvic-only lymphadenectomy (p:0.070), and pelvic and paraaortic lymphadenectomy (p:0.808). The analysis of the demographic information and the surgical approach showed no statistically significant differences between the groups. The clinical and pathological characteristics of the study, preoperative and postoperative Ca-125 values, and other biochemical and histochemical data (p:0.562–p:0.455) are shown in Table 2. These include tumor grade (p:0.309), perineural involvement (p:0.782), uterine lower segment involvement (p:0.368), depth of myometrial invasion (p:0.565), lymphovascular space invasion (LVSI) (p:0.302), tumor size (cm) median (range) (p:0.595), and cervical involvement (p:0.068). These markers are poor prognostic indicators for EC. Our analyses identified no difference between these predictive indicators when examining both groups. In the same table, estrogen receptor (ER) positivity and progesterone receptor (PR) positivity, as well as p16 and p53 positivity were also evaluated as biochemical and histochemical markers and are included as positivity of the ER (p:0.382), positivity of the PR (p:0.242), the presence of p16 (p:0.437), and the presence of p53 (p:0.699). When comparing the two groups,

Table 1. Patient charecteristic demographic variables and surgical variables.

Variable	Adenomyosis		p
	Yes (n=99)	No (n=297)	
Age at surgery, median (range)	60.59	60.50	0.342
Gravity	3.65	3.64	0.947
Nulliparity	4	14	0.448
BMI (kg/cm^2)†	36.42	36.83	0.257
Menapausal status			0.757
Premenopausal (n:%)	10 (10)	33 (11.1)	
Postmenopausal (n: %)	90 (90)	264 (88.9)	
Surgical approach, (n: %)			0.279
Laparoscopy	81 (81.8)	240 (80.8)	
Laparotomy	17 (18.2)	57 (19.2)	
Lymphadenectomy, (n: %)			
Pelvic alone	12 (12.1)	33 (11.1)	0.070
Pelvic and para-aortic	7 (7.4)	30 (10.5)	0.808

p<0.05 accepted as statistically significant. †Body mass index.

Table 2. Tumor characteristics, biochemical and histochemical markers.

Variable	Adenomyosis		p
Tumor grade, n (%)	Yes (n=99)	No (n=297)	0.309
1	27 (27.6)	62 (21.8)	
2	55 (56.1)	157 (53.3)	
3	16 (16.3)	65 (22.9)	
Perineural ınvolvement	21 (21.2)	57 (19.3)	0.782
Uterine lower segment involvement	14 (14.3)	50 (16.9)	0.368
Tumor size (cm) Median (range)	3.31	3.19	0.595
Deep (≥50%) myometrial invasion, n (%)	22 (23.6)	71 (23.7)	0.565
Lymphovascular space involvement, n (%)	89 (89)	252 (84.8)	0.302
Cervical involvement, n (%)	2 (2.02)	12 (4.02)	0.394
Adnexial involvement, n (%)	4 (4.04)	14 (4.6)	0.459
Positive peritoneal cytology, n (%)	4 (4.04)	10 (3.3)	0.496
Preoperative Ca-125 (U/mL)	82	238	0.562
Postoperative Ca-125 (U/mL)	74	221	0.455
ER (+) n (%)†	49 (49)	126 (42.4)	0.382
PR (+) n (%)‡	34 (34)	131 (44)	0.242
P53 existence n (%)	26 (26)	95 (34)	0.699
P16 existence n (%)	12 (12)	46 (15.5)	0.437

p<0.05 accepted as statistically significant.†Estrogen receptor. ‡Progesteron receptor.

no statistically significant differences exist. The group showing PR positive with adenomyosis is higher, but no statistically significant differences were found (p:0.242).

The 5-year DFS and OAS rates between the two groups did not differ in a way that was statistically significant. Median time to recurrence was longer in the adenomyosis-negative group than in the adenomyosis-positive group (61 months vs. 56 months) (p:0.278). For patients with and without adenomyosis, the 5-year OAS was 97 vs. 91.4% (HR 1.51; 95%CI 0.52–4.20; p=0.230) and the 5-year DFS was 94 vs. 92% (HR 1.57; 95%CI 0.51–5.20; p=0.440), respectively. Kaplan-Meier plots are shown in Figure 1. When patients with and without adenomyosis were compared, it was shown that the OAS after 5 years was higher in the adenomyosis-free people. However, no statistically significant changes were found.

DISCUSSION

There has long been interest in the clinical relevance of the coexistence of adenomyosis and EC. Numerous studies have been documented on the relationship between EC and adenomyosis. Our research sought to ascertain whether adenomyosis had a favorable or unfavorable prognostic impact on EC.

Poor prognostic factors for EC include tumor grade, perineural involvement, uterine lower segment involvement, tumor size, depth of myometrial involvement, LVSI, tumor size (cm), cervical involvement, positive peritoneal cytology, and stage of the disease. When these poor prognostic indicators were examined, some studies found that groups with adenomyosis had a worse prognosis than those without adenomyosis[11]. However, in our investigation, no statistically significant difference was discovered.

In one study, OAS in EC with adenomyosis was evaluated as relatively higher than OAS reports in EC alone[12]. This favorable prognostic outcome could be explained by the mechanical role of adenomyosis in preventing cancer invasion through the hypertrophic and hyperplastic myometrial stroma that surrounds it[11]. When cases of EC that developed from adenomyosis were examined in a meta-analysis, it was discovered that the effects of poor prognostic indicators were amplified by deep myometrial tumor involvement, high-grade, complicated stage, and the presence of positive node metastases[13]. In our research, we demonstrated that the prognosis of the disease is unaffected by the existence of adenomyosis in EC.

Although the exact cause of malignant transformation in adenomyosis is still unknown, several writers have suggested

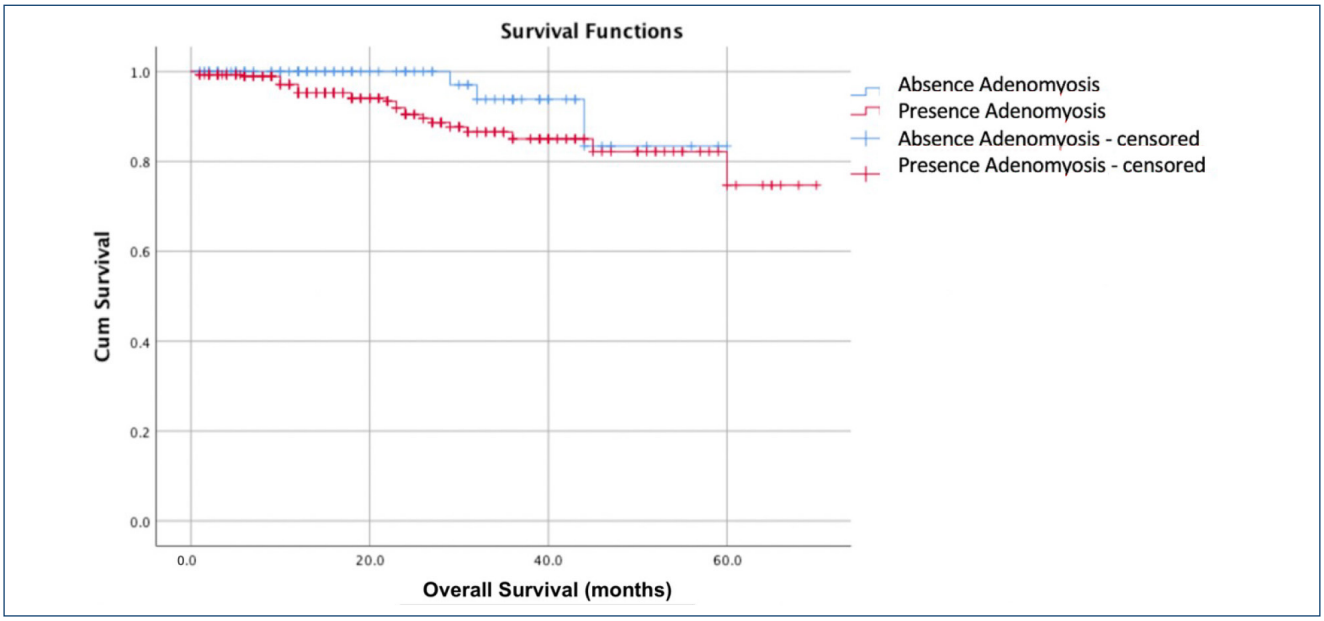

Figure 1. Overall survival curve for the groups.

that genetic and epigenetic factors may be involved. Due to the absence of an anatomic set in the basal part of endometrial tissue, cancer first develops within the myometrial part and smoothly spreads to the myometrial stromal layer[14]. Cancer that has directly invaded the myometrial stromal tissue extends rapidly to the lymphatic and circulatory systems. However, many molecular elements of the malignant development of adenomyosis remain unknown. The relationship between adenomyosis and the disruption of heterozygosity in the DNA mismatch repair gene has only been briefly described in research[15].

Our results suggest that the superior EC prognosis of patients with adenomyosis given to individuals without adenomyosis is not explained by clinical characteristics. After the establishment of the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) and The Cancer Genome Atlas (TCGA) Research Network discoveries, EC may now be divided into four molecular prognostic categories: mismatch repair defective, POLE-mutated, p53-mutated, and p53 wild-type. Groups with POLE mutations and p53 wild-type patients have improved prognoses[16]. Immunohistochemical and hematological markers are important indicators in determining the prognosis of EC[17,18]. Additionally, we assessed the positivity of p53 and p16 in groups with and without adenomyosis. When we compared the two groups, we were unable to detect any statistically significant difference.

A few clinical characteristics have been recognized as EC prognostic indicators[17]. Particularly, it has been found that parous EC women have a much better prognosis than nulliparous women[13]. Age has also been demonstrated to be associated with the prognosis for EC; according to a German population-based investigation, 5-year relative survival fell from 90.0% in the age group of 15–49 years to 74.8% in the age group of over 70 years[19]. When these factors were compared between the two groups in our study, there was no statistically significant difference between them, in contrast to the demographic literature data mentioned above.

Additionally, in EC patients, a greater ER/PR expression status was linked to a better DFS[20]. In our study, we assessed the positivity of ER and PR in both groups. Patients with PR-positive adenomyosis experienced OAS more frequently. However, no statistically significant change was found.

Due to the limited scope of the current investigation, only pathological examinations of women who had been treated with surgery for EC were carried out. The group with adenomyosis was chosen within these findings and contrasted with the group that could not be tracked in a blind manner. This study compared the impact of adenomyosis on EC and observed the p16 and p53 status.

Our research has some drawbacks. First, there is a deficiency of pathological evaluation to differentiate between ECs with adenomyosis and ECs developing from adenomyosis foci. These two disorders are histopathologically and clinically diverse, with different diagnostic criteria and biological characteristics. Histologically speaking, EC emerging in adenomyosis (EC-AIA) is identified by the presence of adenocarcinoma in the epithelium of the adenomyosis foci but not in the typically located

endometrium. In summary, the key difference between these two entities is whether EC is present in the eutopic endometrium[13]. ECs-AIA are strongly related to weak DFS, according to a recent comprehensive analysis comparing cancer results between ECs coexisting with adenomyosis and ECs-AIA. This finding was made after checking for grade, stage of the disease, and histotype[13]. Nevertheless, the rate of EC formation from adenomyosis, as demonstrated in this study, is less than 1%. This meta-analysis only includes case reports for EC, which arises from the backdrop of adenomyosis and exhibits poor prognostic features. Second, our study did not allow us to assess POLE mutations. We think that one of the crucial conditions for upcoming research on EC is the examination of the POLE mutation.

Our research concluded that adenomyosis is not significantly linked to the development of cancer. These results lead us to recommend that the presence of adenomyosis cannot be considered or further studied as a prognostic factor in EC.

AUTHORS' CONTRIBUTIONS

EŞ: Investigation, Methodology, Software, Writing – Original draft. **SY:** Methodology, Writing – Original draft, Writing-review &editing. **SK:** Data curation, Methodology, Visualization. **SG:** Conceptualization, Formal Analysis. **ÖAY:** Conceptualization, Formal Analysis, Software. **İAÖ:** Formal Analysis, Resources, Supervision. **LY:** Investigation, Supervision.

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