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Does Endometriosis Impact the Prognosis of Endometrial Cancer?

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ABSTRACT Objective: Despite the well-known relationship between endometriosis and the risk and prognosis of ovarian cancer, studies on the association the two are rare. Moreover, the impact of endometriosis on the prognosis of endometrial cancer has not been described in the literature. In this study, we attempted to investigate whether endometriosis had an effect on the prognosis of endometrial cancer. **Material and Methods:** This retrospective study was carried out on data from endometrial cancer patients between January 1996 and February 2016 at the Gynecological Oncology Department of Çukurova University Balcalı Hospital in Adana, Turkey. The pathological reports of 920 cases, operated after the diagnosis of endometrial cancer, were screened. Among these cases, 764 patients were found to be eligible for enrollment in this study. The patients were distributed into two groups based on the presence or absence of endometriosis in the pathological materials. The prognosis of the groups was compared using the Kaplan-Meier method. **Results:** The endometriosis group was associated with younger age, less parity, more infertility, and a higher risk of simultaneous ovarian cancer. There were non-significant differences between the groups regarding pathological risk factors such as myometrial invasion, lymphovascular space involvement, lymph node positivity, and stage of progression. No recurrences or deaths were observed in the endometriosis group, although this observation was not statistically significant. **Conclusion:** It is suggested that endometriosis does not influence the prognosis of endometrial cancer. However, a conclusive assessment could not be made by this study alone and, therefore, further studies are needed and researchers are encouraged to focus more on this subject.

Keywords: Endometrial cancer; endometriosis; endometriosis-associated cancers

Endometriosis, which is poorly understood in a pathophysiological sense, is a hormone-dependent inflammatory chronic gynecological disease. It is described as the presence of ectopic endometrial glands and stroma outside the uterine cavity and is associated with pelvic pain, dysmenorrhea, and infertility.[1] Retrograde menstruation, menstrual tissue implantation, and impaired immune response are the most commonly observed conditions. Endometriosis is a fairly common condition, prevalent in ~10% of the women of reproductive age. An estimated 176 million women are affected by this disease worldwide.[2] An increase in the overall cancer incidence in patients with endometriosis has been reported by various studies. However, little is known about the effect of endometriosis on cancer survival.[3]

Most of the previous investigations on the impact of endometriosis on cancer had focused on its relation to ovarian cancer. Therefore, while the relationship between endometriosis and ovarian cancer is well known, its as-

sociation with other malignancies remains controversial. Recently, clear cell endometrioid and seromucinous ovarian carcinomas were accepted as endometriosis-associated ovarian cancers (EAOC). The endometrioid subtype is known to be the most commonly associated histopathologic type with simultaneous endometrial and ovarian cancers. Nearly 30% of the simultaneous cases were reported to harbor endometriosis.[4-6] Both endometriosis and endometrial cancer have the same origin; they have an identical molecular profile and etiological mechanisms such as chronic inflammation and the estrogen effect. Therefore, it is possible that endometriosis might affect the risk and prognosis of endometrial cancer.[4,7-9]

Despite these facts, due attention has not been given to the endometriosis-endometrial cancer association. To the best of our knowledge, no study in the literature has discussed the impact of endometriosis on the prognosis of endometrial cancer. Hence, this paper investigates the possible impact of endometriosis on the prognosis of endometrial cancer. For this purpose, we retrospectively analyzed the cases of endometrial cancer over the last 20 years at our center. In addition, the subgroups for endometrioid and non-endometrioid endometrial cancer cases were compared.

MATERIAL AND METHODS

This study was carried out on patients of endometrial cancer that were operated at the Gynecological Oncology Department of a Tertiary University Hospital between January 1996 and February 2016. The study was conducted in accordance with the Helsinki Declaration. Ethical approval was not required for this study because of its retrospective nature. Written informed consent was obtained from all the participants of the study. The electronic and archival records were retrospectively reviewed and 920 endometrial cancer patients that were operated at our clinic during this period were identified. Among them, detailed pathology records of 764 cases were obtained and utilized for this study.

The demographic, clinicopathologic, and follow-up data of the patients were recorded. All these cases were operated and pathologically evaluated at the same center by expert gynecological pathologists. The major surgical procedures involved total hysterectomy with bilateral salpingo-oophorectomy (via laparotomy or laparoscopy) and pelvic-para-aortic lymphadenectomy (except those with low risk). Omentectomy was performed in the non-endometrioid histologies. FIGO 2009 guidelines were used for staging. All the pathological reports of the operated cases were reviewed to identify the presence of endometriosis in the surgical specimens. The patients were then distributed into two groups based on the presence or absence of endometriosis in the pathological materials. Only the diagnosis of endometriosis that was proven using histopathology was taken into account. The patients were followed up every three months for the first two years after the operation, every six months for the next three years, and annually thereafter. The period in months between the dates of histopathological diagnosis and recurrence was considered as disease-free survival (DFS), and from diagnosis to the date of death as the overall survival (OS).

The descriptive statistics used were mean ±standard deviation, median, and minimum-maximum values. Categorical data were analyzed using Chi-square or Fisher's exact tests. Mann-Whitney U test was performed for analysis of the numerical data. Kaplan-Meier method was followed to test the effect of endometriosis on survival. The differences between survival curves were evaluated using the log-rank test. The statistical software SPSS version 23.0 (IBM, Armonk, NY, USA) was used for all analyses.

RESULTS

During the study period, 920 endometrial cancer patients were operated at our clinic. Among them, the detailed pathological records of 764 cases were obtained and endometriosis was reported in 17 (2.2%) of them. The average and median age of all the patients was 57.2±10.5 years and 58 (27-91) years, respectively. Median parity of the patients was 3 (0-15). Mean ages of the endometriosis and non-endometriosis groups were 50.59±8.3 and 57.28±10.2, respectively. There was a significant

difference in the mean age of both groups (p=0.007). The Body Mass Indices (BMI) of both groups were similar (P=0.530). The clinicopathological characteristics of the patients are demonstrated in Table 1.

The percentages of premenopausal patients in the endometriosis and non-endometriosis groups were 35.3% and 20.3%, respectively. The proportions of premenopausal patients were statistically similar (p=0.132). The percentage of infertility-linked cases in the endometriosis and non-endometriosis groups were 35.3% and 14.5%, respectively, showing a significant difference between groups (p=0.017). In the endometriosis group, there were three (17.6%) cases of simultaneous ovarian cancer, whereas 35 (4.8%) cases were recorded in the non-endometriosis group. This difference was found to be statistically significant (p=0.018).

Both the groups had similar rates of endometrioid (70.6% versus 76.5%) and non-en-

TABLE 1: Demographic and clinical characteristics of patients.

Variable		Endometriosis N (%)	Non-endometriosis N (%)	P
Age	Mean±SD	50.59±8.3	57.28±10.3	0.007
Body mass index	Mean±SD	33.88±5.4	35.53±7.4	0.652
Parity	Median (min.-max.)	1 (0-9)	3 (0-15)	0.002
Menopausal status	Premenopause	6 (35.3)	151 (20.3)	0.132
	Postmenopause	11 (64.7)	592 (79.7)	
Infertility	No	11 (64.7)	632 (85.5)	0.017
	Yes	6 (35.3)	107 (14.5)	
Synchronous ovarian tumor	No	14 (82.4)	690 (95.2)	0.018
	Yes	3 (17.6)	35 (4.8)	
Histology	Endometrioid	12 (70.6)	566 (76.5)	0.571
	Non-endometrioid	5 (29.4)	174 (23.5)	
Stage	Stage 1-2	12 (70.6)	617 (84.2)	0.132
	Stage 3-4	5 (29.4)	116 (15.8)	
Grade	1	10 (66.7)	345 (54.0)	0.375
	2	3 (20.0)	238 (37.2)	
	3	2 (13.3)	56 (8.8)	
Myometrial invasion	<50	12 (75.0)	485 (66.4)	0.473
	≥50	4 (25.0)	245 (33.6)	
Lymphovascular space invasion	No	12 (70.6)	471 (63.9)	0.570
	Yes	5 (29.4)	266 (36.1)	
Cytology	Negative	3 (17.6)	117 (16.2)	0.809
	Positive	0 (0.0)	17 (2.4)	
	Wasn't taken	14 (82.4)	587 (81.4)	
Lymph node involvement	Negative	14 (82.4)	658 (89.6)	0.333
	Positive	3 (17.6)	76 (10.4)	
Omental metastasis	No	3 (17.6)	184 (25.0)	0.303
	Yes	2 (11.8)	32 (4.3)	
	No omentectomy	12 (70.6)	521 (70.7)	
Adjuvant treatment	No	9 (52.9)	436 (58.9)	0.621
	Yes	8 (47.1)	304 (41.1)	
Recurrence	No	17 (100)	726 (97.8)	0.541
	Yes	0 (0.0)	16 (2.2)	
Life status	Alive	17 (100)	579 (86.5)	0.105
	Ex	0 (0.0)	90 (13.5)	

dometrioid (29.4% versus 23.5%) histology (p=0.571). The tumor was confined to the uterus (stage 1-2) in 70.6% and 84.2% of the endometriosis and non-endometriosis groups, respectively, and the difference was not statistically significant. The distribution of tumor grade between the groups was also not significant (p=0.375). Myometrial invasion of ≥50% was observed in 25% of the endometriosis and 33.6% of the non-endometriosis group, which was not significantly different (p=0.473). Lymphovascular space invasion (LVSI) was reported in 29.4% and 36.1% of the endometriosis and non-endometriosis groups, respectively (p=0.570). The occurrence of positive cytology between groups (0% versus 2.4%) was statistically similar. Lymph node (LN) involvement was reported in 17.6% of the endometriosis and 10.4% of the non-endometriosis groups, and these rates were not significantly different. Omental metastases were observed in 11.8% and 4.3% of the endometriosis and non-endometriosis groups, respectively, which were not significantly different (p=0.303). Statistically similar rates of adjuvant treatments were applied to both the groups (47.1% versus 41.1%). No recurrence in the endometriosis group and 2.2% recurrence in the non-endometriosis group were recorded, but this difference was statistically nonsignificant. While 13.5% of the non-endometriosis group patients died, no death was reported among those in the endometriosis group. However, this observation was not statistically significant (p=0.105).

The average follow-up period of the cohort was 51 months. The mean survival period for all the endometrial cancer cases was 191.2±10.5 months (95% CI=170.7-211.8). No deaths were observed in the endometriosis group during the follow-up period. The 5-year and 10-year survival rates in the non-endometriosis group were 86% and 74%, respectively. The period and rate of survival between endometriosis and non-endometriosis groups were not statistically significant (p=0.171) (Figure 1).

The survival rates of the endometrioid and non-endometrioid endometrial cancer subgroups were also compared and were found to be statistically similar. The p-values for the endometrioid and non-endometrioid subgroups were 0.315 and 0.341, respectively.

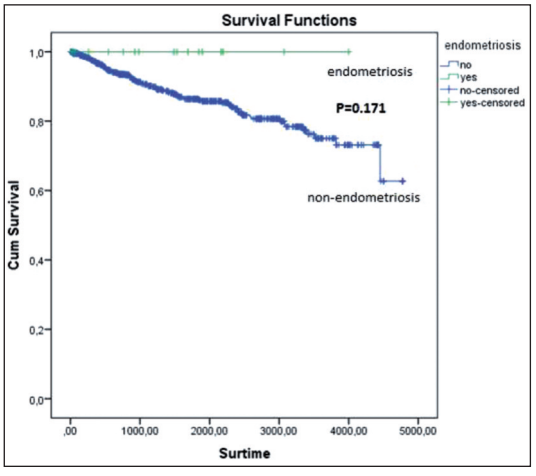

FIGURE 1: Survival curves of the groups.

DISCUSSION

Despite the association of endometriosis with ovarian cancer being widely investigated, that with endometrial cancer has been rarely studied and with conflicting results.[4,10,11] While some studies have reported an increased risk of endometrial cancer associated with endometriosis, others have reported contradictory findings.[4,7,10-18] Moreover, two studies reported a non-significant decrease, while one study reported a significant decrease in the risk of endometrial cancer associated with endometriosis.[18-20]

Three large case-control studies from Taiwan (n=15,488), Australia (n=1,399), and Denmark (n=1,398) reported an increased risk of endometrial cancer in the cases of endometriosis.[4,14,15] However, this risk reflected a higher chance of detecting endometrial cancer among women with endometriosis more than the actual risk.s reported in a recent, large-volume prospective cohort (n=97,109) from the USA.[7]

Kok et al. published a population-based study on the relation between endometriosis and the risk of developing several cancers, including endometrial cancer.[21] They observed a significantly increased risk of endometrial cancer among women

with endometriosis and/or adenomyosis. However, it was evident that histopathology was not the main diagnostic tool in this study, especially in the adenomyosis patients, thus making the starting point of the study and its results questionable.

Munksgaard and Blaakaer reviewed seven population-based cohorts that investigated the association between the risk of endometrial cancer and endometriosis and reported that no clear association was observed in these studies.[13] Although some studies did point to a possible association, they concluded that the relatively small sample sizes precluded any definitive interpretation about the possible association.

Our study was different in its nature and design from the above-mentioned studies. The cases of endometrial cancer that were operated at our center were retrospectively reviewed, and those with histopathological diagnosis of endometriosis (17 patients) were compared with the non-endometriosis patients. To the best of our knowledge, no previous studies in the literature had focused on the association between endometriosis and endometrial cancer prognosis. It was observed that the patients in the endometriosis group were significantly younger than the non-endometriosis patients. The median value of parity in the endometriosis group was lesser, possibly due to the close relationship between endometriosis and infertility.

About 75% of the cases in each group showed endometrioid histology. The tumor histology of both groups was similar. The patients in the endometriosis group demonstrated a higher but statistically insignificant extra-uterine spread of the tumor (stage 3-4, 29.4% versus 14.8%). In addition, the tumor grade distribution was similar in both groups (p=0.375). Frequencies of myometrial invasion of at least 50% and LVSI were observed to be lesser by 8.6% and 6.7% in the endometriosis group, although this difference was not statistically significant. LN involvement was higher by 7.3% in the endometriosis group than the non-endometriosis group, although this difference was statistically nonsignificant. It is possible that the higher LN positivity and the occurrence of extra-uterine disease in the endometriosis group make the adjuvant treatments more suitable for this group (47.1% versus 41.1%). Despite these negative factors, no recurrences or deaths were observed in the endometriosis patients, when compared to the 2.2% rate of recurrence and 13.5% rate of death in the non-endometriosis group. Nevertheless, the rates of recurrence or survival status were not significantly different between the groups. The average follow-up period of the cohort was 51 months. The mean survival period for all the cases of endometrial cancer was 191.2±10.5 months (170.7-211.8; 95% CI). As no deaths were observed in the endometriosis group during the follow-up period, survival rates could not be calculated for this group. On the other hand, 5-year and 10-year survival rates in the non-endometriosis group were 86% and 74%, respectively. However, survival in both groups was statistically similar (p=0.171). In addition, when a subgroup analysis was made for the endometrioid and non-endometrioid endometrial cancer histology, no significant difference in survival was observed between the endometriosis and non-endometriosis patients.

As expected, the endometriosis group showed a significant association with infertility and synchronous ovarian cancer. Both these conditions were significantly higher in the endometriosis group compared to the non-endometriosis group.

The strengths of this study were the fairly large number of endometrial cancer cases, as well as the length of the study period at the same center with the same surgical procedures and pathology team. These factors increased the consistency and reliability of the results of this study. However, the retrospective nature of this study and the relatively small size of the endometriosis group were the main weaknesses of this study.

CONCLUSION

In this study, it was observed that the prognosis of endometrial cancer patients was neither positively nor negatively affected by endometriosis. How-

ever, the relatively small sample size in the endometriosis group precludes making any definitive conclusions. Therefore, further studies should be encouraged in this field.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ghanim Khatib, Derya Gümürdülü, Mehmet Ali Vardar;* ***Design:*** *Ghanim Khatib, Ümran Küçükgöz Güleç;* ***Control/Supervision:*** *Mehmet Ali Vardar, Ahmet Barış Güzel;* ***Data Collection and/or Processing:*** *Ghanim Khatib, İsa Temur, Mete Sucu, Emine Bağır;* ***Analysis and/or Interpretation:*** *Ghanim Khatib, Emine Bağır, Ümran Küçükgöz Güleç;* ***Literature Review:*** *Ghanim Khatib, İsa Temur;* ***Writing the Article:*** *Ghanim Khatib;* ***Critical Review:*** *Ümran Küçükgöz Güleç, Ahmet Barış Güzel, Mehmet Ali Vardar;* ***References and Fundings:*** *Ghanim Khatib, İsa Temur, Mete Sucu, Emine Bağır.*

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