Investigation of the Predictive Factors of Recurrent Ovarian Mucinous Cystadenoma

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ABSTRACT

OBJECTIVE: Rapid growth patterns and recurrence with variable rates have been reported in the literature, making mucinous cystadenomas different from other ovarian benign neoplasms. The study aimed to predict and prevent recurrence based on the obtained results.

STUDY DESIGN: In this case-control study among the 2,341 patients who underwent surgery for ovarian cysts, 221 met the inclusion criteria. The 221 patients diagnosed with mucinous cystadenoma were categorized into two groups: 14 patients (6.3%) with recurrence and 207 patients (93.7%) without recurrence. Patients in these groups were compared in terms of demographic characteristics, ovarian cyst size, operative technique, type of surgery (oophorectomy or cystectomy), Ca19-9, CA125, and CEA values of the patients, and duration of postoperative follow-up.

RESULTS: The mean age was statistically lower in the group with recurrence $(27\pm5 \text{ vs } 44\pm14; \text{ p}<0.001)$. The follow-up period of recurrent cases was significantly longer (6.8 ± 3.5 vs 4.9 ± 2.2 years; p=0.045). The recurrence rate was significantly higher in patients who underwent cystectomy (p<0.001; odds ratio: 22.8). When all patients were examined, cystectomy was preferred in younger patients [31 (18-65) vs 48 (18-81); p<0.001]. According to regression analysis, cystectomy alone is an independent risk factor (p=0.041).

CONCLUSION: Unlike conventional ovarian cystadenomas, mucinous cystadenomas should be followed up owing to the possibility of recurrence, especially when detected at an early age. Since cystectomy is the only independent risk factor, oophorectomy should be the primary treatment for patients >40 years of age who have no desire for childbearing.

Keywords: Mucinous cystadenoma; Mucinous neoplasm; Ovarian cyst; Ovary neoplasm; Recurrences

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Introduction

Surface epithelial tumors comprise 65-70% of all ovarian tumors. These tumors originate from the fallopian tubes, ovaries, endocervix, and endometrium. Mucinous cystadenomas account for approximately 15-20% of these tumors. Owing to their rapid growth pattern, giant masses are often detected late; however, they are benign (1). The rapid growth pattern of mucinous cystadenomas makes it difficult to distinguish them from malignant tumors. Eighty percent of mucinous ovarian tumors with mucin-secreting surface epithelium are also benign. When examined pathologically, mucinous cystadenoma is typically found to be multicystic and does not show surface involvement (2). Approximately 90% of mucinous cystadenomas involve only one ovary (3).

When mucinous tumors (benign, malignant, or borderline) are examined radiologically, their average size is 18 cm when diagnosed at the time of the first symptom. These tumors appear as honeycomb-like loculi and are multiloculated. They contain solid components of varying complexity according to their type (4). A dermoid cyst or Brenner tumor may accompany approximately 10% of mucinous cystadenomas and cystadenofibromas (5). Patients with adnexal masses >10 cm in

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size undergo cystectomy or oophorectomy owing to the approximately 10% chance of malignancy (6). Although mucinous cystadenomas are benign according to pathological examination, recurrence has been reported in the literature at variable rates.

In this study, we examined patients who underwent surgery following the diagnosis of mucinous cystadenoma and investigated the differences in demographic characteristics, follow-up periods, tumor markers, mass sizes, and operative techniques between those with and without recurrence. The study aimed to predict and prevent recurrence, based on the obtained results.

Material and Method

Between 2010 and 2023, a total of 2,341 patients who underwent surgery for ovarian cysts at tertiary care university hospitals were retrospectively analyzed using hospital archive records. The inclusion criterion for the study was a diagnosis of mucinous cystadenoma confirmed by pathological examination of the ovary. Patients with an indication for hysterectomy were not included in the study, and only those planned for ovarian cystectomy or oophorectomy were included. Cases diagnosed with previous endometriosis and having ovarian cysts except for mucinous cystadenoma cases were excluded (5). Patients with missing demographic data, operation notes, tumor markers, details about preoperative imaging methods, and individuals <18 years of age were excluded from the study. Local ethics committee approval for the study was received from our center (Meeting date: 21/09/2023, Decision number: 0355). All procedures performed were in accordance with the ethical standards of the institutional committee and with the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards.

Two hundred and twenty-one patients included in this casecontrol study were categorized into two groups: 14 patients (6.3%) with recurrence and 207 patients (93.7%) without recurrence. Demographic characteristics of the patients, such as age, comorbidity, and number of pregnancies, were recorded. Patients in these groups were compared in terms of demographic characteristics, ovarian cyst size at the time of diagnosis, operative technique (laparoscopy or laparotomy), type of surgery (oophorectomy or cystectomy), and duration of postoperative follow-up. The operation technique and type were determined by evaluating the patient's risks such as previous abdominal surgery, suspicion of cancer, mass size, and desire for childbearing. The possible relationship between recurrence and cystectomy or laparoscopy was analyzed in the study. The difference between the mean preoperative CA 19-9, CA125, and CEA values of the patients in both groups was also compared.

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL., USA). Frequency analyses were performed for demographic data and other independent variables, and medians means, and standard deviations were

calculated. After checking for normality and homogeneity of variances, differences in the mean age, follow-up period, mass size, and tumor markers between patients with and without recurrence were evaluated using the Mann-Whitney U test. The relationship between cystectomy and recurrence and that between laparoscopy and recurrence were evaluated using Fisher's exact test. The relationship between the type of surgery and the patients who underwent cystectomy was analyzed using the Pearson chi-square test. The Mann-Whitney U test was used to evaluate the difference in mean age and mass size between patients who underwent cystectomy and those who underwent oophorectomy. Differences in the mean follow-up period, mass size, and age at the first operation between those with and without recurrence in cystectomized patients were analyzed using the student's t-test. Logistic regression analysis was used to define predictive factors. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). A p-value of <0.05 was considered to indicate statistical significance.

Results

When demographic characteristics were evaluated, the mean patient age was 43 ± 14 years, and the follow-up period was 5 ± 2 years in all patients. The median gravidity was 2 (range 0–11). When comorbidities were evaluated, three patients had hypertension and five patients had diabetes mellitus. The mean mass size at the last preoperative ultrasound or magnetic resonance examination was 11.3 ± 6.5 cm. Recurrence was detected in 14 (6.3%) of the 221 patients with mucinous cystadenoma pathology, and reoperation was performed. Of the patients with recurrence, 5 (35%) underwent repeat cystectomy to preserve ovarian reserves, whereas oophorectomy was preferred by most patients.

Oophorectomy was performed in 166 (75.1%) of all patients in the first operation and ovarian cystectomy was performed in 55 (24.9%) patients. Although oophorectomy was performed in 2 (14%) patients with recurrence, mucinous cystadenoma occurred in the other ovary. A recurrence was detected in the other ovary of these two patients who underwent unilateral oophorectomy 2 years and 5 years later, respectively. The majority of patients with recurrence (n=9, 64.2%) underwent laparotomy. However, there was no significant relationship between recurrence and operative technique (laparoscopy, n=71, 32.1%; laparotomy n=150, 67.9%) (p=1). The mean age was significantly lower in patients with recurrence (27 ± 5) than in those without recurrence (44 ± 14) (p<0.001). The mean duration of follow-up was significantly longer in patients with recurrence (6.8 ± 3.5 years) than in those without recurrence $(4.9 \pm 2.2 \text{ years})$ (p=0.045). While the mean size of the mass in patients with recurrence was 12.5 cm, the size of the mass in the group without recurrence was 11.2 cm (p=0.353). The mean CA-125 level was 29.4 in the group with recurrence and 12 in the group without recurrence (p=0.766). The mean CEA level was 12 in the group with recurrence and 12.5 in the

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group without recurrence (p=0.899). The mean CA 19-9 level was 37.3 ± 14.6 in the group with recurrence and 32.8 ± 14.0 in the group without recurrence (p=0.275). Recurrence in the other ovary was observed in 2 patients who underwent ophorectomy and 12 patients who underwent cystectomy. The recurrence rate was significantly higher in patients who underwent cystectomy (p<0.001). Demographic data, follow-up time, mass size, operation technique, and type according to the groups are summarized in Table I. There was no significant difference (p=0.21) in the mass size of patients who underwent cystectomy (9.8 cm, range: 5-27) and those who underwent ophorectomy (10 cm, range: 1-40).

Subgroup analysis was performed for the patients who underwent ovarian cystectomy owing to mucinous cystadenoma, and no significant differences were found in terms of the duration of follow-up (p=0.051) and mass size (p=0.152) between patients with and without recurrence. There was no relationship between cystectomy and recurrence (p=0.794). When the ages at the time of ovarian cystectomy were compared, it was found that patients with recurrence (27 ± 4.9) were significantly younger than those without recurrence (32 ± 10.1) (p=0.027) (Table II). Regression analysis with possible risk factors for recurrence development is given in Table III. Cystectomy was found to be the only independent risk factor (OR: 2.3, 95% CI: 1.4-4.7).

Discussion

In the study, the recurrence rate was 6.3% in patients with epithelial ovarian tumors diagnosed as mucinous cystadenoma. The risk of recurrence was found to be higher in patients who were diagnosed at an earlier age and in those with a longer follow-up period. Since ovarian cystectomy alone in-

Table I: Comparison of cases with and without recurrent mucinous cystadenoma.

	Recurrence	Non-Recurrence	р
	(n=14 (6.3%))	(n=207 (93.7%))	-
Age (mean ± SD)	27 ± 5	44 ± 14	p<0.001α
Gravida (median (range))	2 (0-4)	2(0-11)	n/a
Co-morbidity (n (%))	DM:1 (7%)	DM:4 (2%)	n/a
	HT:1 (7%)	HT:2 (1%)	
Mass size (cm) (mean ± SD)	12.5 ± 6.0	11.2 ± 6.6	p=0.353 ^β
CA125 (mean ± SD)	12.0 ± 2.5	29.4 ± 56.6	р=0.766 ^в
CEA (mean ± SD)	12.0 ± 2.2	12.5 ± 1.7	р=0.899 ^в
CA19-9 (mean ± SD)	37.3 ± 14.6	32.8 ± 14.0	p=0.275 ^β
Follow-Up (year) (mean ± SD)	6.8 ± 3.5	4.9 ± 2.2	p=0.045 ^µ
Surgery Technique (n (%))			p=1 ^Ω
Laparotomy	9 (64.2%)	141 (68.1%)	
Laparoscopy	5 (35.8%)	66 (31.9%)	
Surgical Procedure (n (%))		. ,	p<0.001*
Oophorectomy	2 (4.2%)	164 (79.2%)	-
Cystectomy	12 (85.8%)	43 (20.8%)	

 α , β , μ =Mann Whitney U Test; Ω , *=Fisher Exact Test, n/a: Not applicable; DM: Diabetes mellitus, HT: Hypertension

Table II: Subo	roup ana	vsis of	patients who	preferred	ovarian c	vstectom	/ due to	mucinous c	vstadenoma
		,				,			,

	Recurrence (n=12 (21.8%))	Non-Recurrence (n=43 (78.2%))	р
Age (mean ± SD)	27±4.9	32±10.1	0.027
Mass size (cm) (mean ± SD)	11.8 ±5.3	9.7± 4.6	0.152
Follow-Up (year) (mean ± SD)	6.9 ± 3.8	4.6±1.8	0.051

*= Student T Test

Table III: Regression analysis of factors that may predict the risk of relapse

		Univariate			Multivariate		
	OR	95% CI	р	OR	95% CI	р	
Appendectomy	0.9	0.3-2.7	0.744	1.3	0.4-2.6	0.782	
Laparoscopy	1.3	0.4-2.4	0.416	1.4	0.5-2.9	0.548	
Cystectomy	2.8	1.6-7.6	0.038	2.3	1.4-4.7	0.041	
Postmenopausal	1.4	0.8-2.1	0.082	1.2	0.7-1.9	0.094	
High Ca125 level (>35)	1.2	0.4-1.9	0.679	1.3	0.4-2.3	0.512	
Large mass (>10 cm)	2.1	0.8-4.4	0.093	1.8	0.8-3.7	0.106	

creases recurrence, oophorectomy should be the first method in cases who have completed their desire to have children.

Although oophorectomy is recommended by some authors to prevent recurrence, in our study, mucinous cystadenoma occurred in the other ovary despite oophorectomy in two patients (7). Since recurrence is 2.8 times more likely in patients who have undergone cystectomy, bilateral oophorectomy should be considered a priority in patients with mucinous cystadenomas. Choosing oophorectomy over cystectomy as a treatment option will be difficult, especially for young patients who have not completed their childbearing. Patients who prefer cystectomy should be informed in detail about the possibility of recurrence, and their consent should be obtained.

Although young age at diagnosis and having previously undergone ovarian cystectomy aided in predicting recurrence, tumor markers were of no use. Tumor markers are only useful in differentiating malignant from benign tumors (8).

When examining patients with recurrence in the literature, a 20-year-old patient from Türkiye had undergone left oophorectomy and right ovarian cystectomy during the first operation. The diagnosis was mucinous cystadenoma in the pathological examination, in which 25 detailed sections were taken. The patient underwent a right ovarian cystectomy 7 months later for the same reason. Fourteen months after the previous operation, the patient underwent a third surgery due to mucinous cystadenoma, during which hysterectomy and right oophorectomy were performed (9). None of our patients underwent a third operation. Beroukhim et al. found that two patients who underwent cystectomy for mucinous cystadenoma in adolescence progressed to mucinous borderline ovarian tumors 5 and 17 months after surgery. They reported no recurrence in these patients after unilateral oophorectomy for at least 2 years of follow-up (10). Similar to our observations, their study shows that mucinous ovarian tumors are highly likely to recur at a young age and even exhibit progression. Although cystectomy is preferred, especially in young patients, as it increases the risk of recurrence, cystectomy causes an increase in state health insurance payments, loss of workforce, and a decrease in quality of life.

In our study and the literature, the earliest recurrence in patients operated for mucinous cystadenoma was noted at 2 months (11). Therefore, we think that the first postoperative follow-up period of patients who are to be operated for mucinous cystadenoma should be at least 2 months. In our clinic, we perform subsequent follow-ups at postoperative 6 months and 1 year.

Intraoperative frozen section examination is performed for large epithelial tumors with a multicystic appearance. According to Taskiran et al., the misdiagnosis rate in frozen section examination in epithelial ovarian tumors was 4.8%, whereas it was 17.4% in mucinous ovarian tumors (12). In mucinous ovarian tumors with multiple foci, performing multiple section examinations may increase the specificity and sensitivity of histopathological diagnosis. The possibility of misdiagnosis increases, especially in mucinous ovarian tumors of >13 cm. In such cases, \geq 4 frozen sections are recommended (13).

In mucinous ovarian tumors, dissemination may occur as a result of the rupture of tumor contents and via surgical instruments or at the site of trocar insertion. To prevent intraoperative spread from the ruptured cyst, it is recommended to remove masses of >10 cm within an endo bag (7). There are conflicting reports about dissemination in the ruptured mucinous cystadenomas alone (14-16). In the literature, the finding of recurrent mucinous neoplasms at the site of uterine Kerr incision or in the neighborhood of the uterus in patients who had undergone oophorectomy without rupture owing to mucinous cystadenoma suggests that this epithelial tumor may have a different pattern of spread (17,18). Due to the retrospective nature of the data analysis, cases of recurrence resulting from spontaneous ovarian cyst rupture could not be included in the results section.

The recurrence of a benign mucinous cystadenoma raises two important questions: Has the malignancy potential of mucinous ovarian tumors that can reach extreme sizes not been adequately evaluated pathologically? Or is the complete resection of a multiloculated mucinous ovarian tumor incomplete? In our study, the identification of mucinous cystadenoma in the other ovary of a patient who had previously undergone oophorectomy, along with the recurrence of mucinous cystadenoma in the same ovary after the first operation by highly experienced gynecologic oncologists (19), suggests that this disease may have a different character from typical cystadenomas.

The strength of our study is that the most recurrent cases of ovarian mucinous cystadenoma in the literature up to date were collected and compared with those without recurrence. The weaknesses of the study include its retrospective nature, which hinders revealing technical differences in the operations, and the absence of long-term follow-up data. Prospective nationwide studies must be conducted in the future to shed light on scientific knowledge.

In conclusion, in cases with suspected mucinous cystadenoma, oophorectomy should be considered as the primary treatment for patients >40 of age who have no desire for childbearing, as cystectomy alone increases the recurrence by 2.8 times. Unlike conventional ovarian cystadenomas, mucinous cystadenomas should be followed up in the postoperative period with serial transvaginal ultrasound examinations owing to the possibility of recurrence.

Declarations

Ethics approval and consent to participate: Consent for using data was taken. The study was reviewed and approved by the ethics committee of Izmir Katip Celebi University (Ethics approval reference number: 0355, Date: 21.09.2023). All proceGynecology Obstetrics & Reproductive Medicine 2024;30(2):138-142

dures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Declaration of conflicts of interest: The authors report no conflicts of interest

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