

## The Value of Ultrasonography and Tumor Markers in the Differential Diagnosis of Postmenopausal Ovarian Cysts

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**Aim:** To evaluate the use of tumor markers in the differentiation of malignant and benign ovarian cysts in the postmenopausal period.

**Materials and Methods:** The study included postmenopausal 46 patients with ovarian cysts that were assessed pre- and postoperatively using CA125 levels, ultrasonographic findings, and histopathological examination at the Obstetrics and Gynecology Clinic, Ankara Atatürk Training and Research Hospital.

**Results:** Mean age of menopause onset was 46 years and mean duration of menopause was 11 years. Histopathological examination revealed that 28.3% of the ovarian cysts were malignant and 71.7% were benign. Of the malignant cysts, 84% were unilateral, with a mean diameter of 74.61 mm; mean diameter of the benign cysts was 58 mm. While 80% of cysts with a high CA125 value were malignant, 20% were benign. Pathological examination revealed that 96.8% of cysts with a normal CA125 value were benign and 3.2% were malignant. Mean CA125 values were 264 U/ml for malignant cysts and 14.2 U/ml for benign cysts. When pathological assessment was based only on ultrasonographic findings, 73.9% of the ovarian cysts were malignant and 26.1% were benign. While unilateral or bilateral localization in the ultrasonography was insignificant, the presence of a solid component was a good predictor of malignancy ( $P = 0.0001$ ).

**Conclusions:** In the differentiation of benign and malignant cysts in postmenopausal women, the presence of a solid component based on ultrasonography, cysts larger than 5-6 cm, and high CA125 values may be used as discriminative criteria. For those patients with cysts that are assumed to be benign follow-up may be an option for reducing the mortality and morbidity associated with surgery.

**Key Words:** Postmenopause, ovarian cysts, tumor markers, ultrasonography

### Postmenopozal Over Kistlerinin Ayırıcı Tanısında Ultrasonografi ve Tümör Belirteçlerinin Değeri

**Amaç:** Postmenopozal dönemde görülen over kistlerinin malign – benign ayırımı yapmak için tümör belirteçlerinin değerlendirilmesi.

**Yöntem ve Gereç:** Ankara Atatürk Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde postmenopozal dönemde tespit edilen 46 over kisti olgusunun pre ve post operatif olarak değerlendirmelerinin CA125 ölçümü, ultrasonografi bulguları ve patolojik inceleme sonuçları ile yapılması.

**Bulgular:** Ortalama menopoz yaşı 46, ortalama menopoz yılı 11 olarak bulundu. Over kistlerinin % 28,3' ü malign, % 71,7' si benign olarak patolojik tetkikleri rapor edildi.

Malign olanların % 84'ü unilateral olup ortalama çapları 74,61 mm, benign olanların ise ortalama çapları 58 mm olarak ölçüldü. CA125 değeri yüksek olanların % 80' i malign % 20'si benign idi. CA125 değeri normal olanların % 96,8'i benign, % 3,2'si malign olarak patolojik tanıları konuldu. Malign olanların ortalama CA125 değeri 264 U/ml, benign olanların 14,2 U/ml bulundu. Yalnızca ultrasonografi sonuçlarına göre patolojiler değerlendirildiğinde % 73,9'u malign, % 26,1'i benign çıktı. Ultrasonografide uni ya da bilateral yerleşiminin önemli olmadığı, solid komponentin malignitede iyi bir gösterge olabileceği tespit edildi ( $P = 0,0001$ ).

**Sonuç:** Postmenopozal kistlerin takibinde benign – malign ayırımının yapılmasında ultrasonografide solid komponent varlığı, kistin boyutunun 5-6 cm den büyük olması ve CA125 değerinin yüksek olması kriter olarak kullanılabilir. Benign düşünülen hastalarda operatif morbidite ve mortaliteyi azaltmak için bekleme tedavisi yapılabilir.

**Anahtar Sözcükler:** Postmenopoz, over kisti, tanı, tümör belirteci, ultrasonografi

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## Introduction

Mortality due to ovarian cancer remains high, with a 5-year survival rate of 50%, despite considerable healthcare developments in recent years (1). Over 70% of ovarian cancers are diagnosed at stage 3-4 (2). The incidence is 0.4-8.9/100,000 among women younger than 40 years, whereas it increases up to 60/100,000 among those aged between 60 and 80 years (3).

While palpable adnexal masses or ovaries in postmenopausal women were previously considered indications for surgery, widespread use of ultrasonographic examination and supplementation with laboratory tests provided the opportunity to only follow up patients with a low risk of malignancy (4). Yet, surgical interventions for early diagnosis of ovarian cancer increase the risk of morbidity and mortality, and may affect decisions concerning surgery.

The aim of the present study was to assess postmenopausal women with cysts using preoperative tumor markers and ultrasonography (USG) to preliminarily differentiate benign and malignant cysts, and to compare this assessment with postoperative results.

## Materials and Methods

The study group included 46 postmenopausal women with adnexal masses that presented to the Obstetrics and Gynecology Clinic, Ankara Atatürk Training and Research Hospital between February 2004 and May 2007. Patients with a previous diagnosis of malignancy were excluded.

Age, menopausal duration, symptoms, laboratory findings, transvaginal ultrasonography (TVUSG) findings, tumor markers (CA125), and postoperative histopathology findings of each patient were recorded. With TVUSG the cysts were assessed for multilocular appearance, bilateral location, presence of septation, papillary structure content, size, and wall structure. Histopathological examination findings were considered the gold standard.

SPSS was used for statistical analyses. Variables with parametric distribution were analyzed with the t test; the Mann-Whitney U test and the Wilcoxon test were used for variables with nonparametric distribution. CA125 values and histopathological examination findings were compared using Fisher's exact test, and ultrasonographic and pathological examination findings were compared

with the McNemar test. P values less than 0.05 with a 95% confidence interval were considered significant.

## Results

Mean age of the patients was  $46 \pm 8.4$  years and mean duration of menopause was  $11.1 \pm 8.6$  years. Mean age of patients with benign and malignant pathology was 61 and 59 years, respectively; the difference was not statistically significant. According to histopathological examination, the prevalence of malignancy was 28.3% and the prevalence of benign cysts was 71.7%. The frequency of unilateral cysts was 84% in patients with malignant pathology and 94% in those with benign masses; the difference was not significant. While the maximum cyst diameter and mean diameter of malignant tumors was 90.61 mm and 74 mm, respectively, the corresponding figures for benign masses were 63.54 mm and 58 mm, respectively.

Among the patients with a high CA125 value (normal values 0-35), 80% of ovarian cysts were malignant and 20% were benign; the corresponding percentages for patients with normal CA125 levels were 96.8% and 3.2%, respectively. There was a significant correlation between CA125 values and pathological findings ( $P = 0.0001$ , Fisher's exact test).

Overall, 28.3% of the patients had high CA125 levels and malignant histopathological results, 67.4% had normal CA125 levels and benign histopathological results, and 4.3% had either normal CA125 levels and malignant cysts or high CA125 values and benign cysts.

Based on TVUSG findings alone, 73.9% of the cysts were malignant and 26.1% were benign (sensitivity 92.3%, specificity 33.3%). The low specificity suggests that 33.3% of patients with benign pathology also had benign ultrasonographic findings (positive predictive value = 35.3%) (negative predictive value = 91.7%). The McNemar test indicated that TVUSG and histopathology results correlated significantly ( $P = 0.0001$ ).

Cysts were unilateral in 93.9% of the patients with benign histopathological findings and in 84.6% of those with malignant histopathological results. There was no significant correlation between histopathological findings and unilateral/bilateral location ( $P = 0.565$ , Fisher's exact test). Solid components were present in 76.9% of patients with malignant histopathological results and in 27.3% of those with benign findings.

Table. Comparison of ultrasonographical and histopathological findings.

			PATHOLOGY		Total
			Malignant	Benign	
	Malignant	Number	12	22	34
		% within USG	35.3%	64.7%	100.0%
		% within pathology	92.3%	66.7%	73.9%
	Benign	Number	1	11	12
		% within USG	8.3%	91.7%	100.0%
		% within pathology	7.7%	33.3%	26.1%
Total	Number	13	33	46	
	% within USG	28.3%	71.7%	100.0%	
	% within pathology	100.0%	100.0%	100.0%	

Histopathological distribution of benign cysts was as follows: benign serous cyst: 66.7%; fibroma: 9.1%; dermoid cyst: 6.1%; cystadenofibroma: 6.1%; serous cystadenoma: 3%; mucinous cystadenoma: 9.1%. For malignant cysts histopathological distribution was as follows: granulosa cell tumor: 15.4%; serous cystadenocarcinoma: 61.5%; mucinous cystadenocarcinoma: 15.1%; transitional cell carcinoma: 2.7%.

**Discussion**

Efforts directed at the early diagnosis of ovarian cancer have resulted in increasing the number of surgical interventions, which has led to a rise in mortality and morbidity. The most widely used modalities for accurate diagnosis are CA125 measurement and TVUSG. The specificity and sensitivity of tumor markers alone are low for all age groups. They are more useful for follow-up than for diagnosis (5). CA125 is a nonspecific marker, which may increase in acute hepatitis, acute pancreatitis, pregnancy, cirrhosis, and systemic lupus erythematosus. The significance of this marker alone in ovarian pathologies in the postmenopausal period is unclear. Tuxen et al. reported that CA125 levels were within the normal range in 10%-20% of patients with ovarian cancer and in about 50% of those with stage 1 lesions

(5). Thus, interpretation of CA125 levels, along with physical findings, was suggested. In the present study CA125 levels were high in 92.3% of malignant cases and normal in 7.7%, which are close to the rates reported in Tuxen's study; however, malignancy should always be considered in patients with a high CA125 level. CA125 levels were high in 80% of cases in a study by Kabawat et al. (6).

TVUSG is the most effective method for showing the presence of postmenopausal ovarian cysts. Sassone et al. reported a morphological scoring system using conventional 'gray scale' TVUSG to facilitate the differentiation of malignant and benign tumors. The sensitivity of the scoring system was 100%, specificity was 83%, positive predictive value (PPV) was 37%, and negative predictive value (NPV) was 100% (7). The corresponding values for TVUSG in the present study were 92.3%, 33.3%, 35.3%, and 91.7%, respectively, and, except for sensitivity, appear to be in accordance with those in Sassone et al.'s study. Fenchel et al. reported that the sensitivity and specificity of TVUSG were 92% and 60%, respectively (8). The TVUSG parameters in the present study were size, solid component, septation, presence of ascites, and uni/bilateral location.

Ovary volume decreases with age in the postmenopausal period. Goswamy et al. examined the volume of the ovaries in 2221 postmenopausal women and noted that ovarian volume decreased with age by a mean  $1.5 \pm 0.5$  cm. Only 10% of postmenopausal women with palpable ovaries had ovarian cancer; the remaining patients had tumors, such as fibromas or Brenner tumors (9).

Considering TVUSG parameters separately in the discrimination of benign and malignant ovarian cysts in the present study, mean size of the benign ovarian cysts was 58 mm. Of the 22 cases with cysts less than 58 mm, only 3 were malignant (true positivity: 87.37%; false positivity 13.63%). In all, 6 cases with cysts greater than 90.6 mm were benign and 5 cases were malignant. Of those patients with cysts 58-90.6 mm, 8 were benign and 5 were malignant. Although the likelihood of malignancy increases with cyst size, size alone is not an indication for surgery.

Of the 17 cases in the present study with septate cysts, 6 were malignant; however, this was not a predictor for malignancy. Solid components were present in 19 patients, of which 10 were malignant and 9 were benign. Overall, 10 of 13 the malignant cases had a solid component. Solid component frequency in malignant cases was 76.92%, which was quite high. The true and false positivity values for the presence of a solid component in the differentiation of malignant and benign cysts were 76.92% and 23.08%, respectively. That is, the presence of a solid component was the second most significant parameter after CA125 level for an accurate diagnosis.

The cysts were bilateral in 4 of our 46 patients; 2 were malignant and 2 were benign. Thus, bilateral location was not a significant criterion for discrimination between malignant and benign cysts. According to TVUSG findings, 4 patients had solid and septated cysts greater

than 58 mm. Similarly, there were 4 patients with cysts greater than 90.6 mm, of which 3 were malignant and 1 was benign. Combining these parameters, false positivity was 25% and true positivity was 75%, with high predictivity. The only case with benign histopathology was a mucinous cystadenoma; however, such cases may not be considered misdiagnosed because they induce high levels of CA125, grow rapidly, mimic malignant cysts in TVUSG, and require surgical intervention despite their benign pathology.

Goldenstein concluded that the incidence of malignancy was low in postmenopausal unilocular cysts less than 5 cm and that they could be followed with serial TVUSG examinations, without surgical intervention (2). Nordo et al. showed that unilocular ovarian cysts less than 50 mm did not change their benign characteristics in 226 postmenopausal women over a 5-year follow-up period, and concluded that patients did not require surgical intervention if the cyst did not increase in size and serum CA125 levels were normal (10). Grab et al. compared TVUSG with MRI and PET for the differentiation of malignant and benign ovarian cysts, and suggested that while they had similar specificity, TVUSG was more sensitive. Combining the 3 techniques may increase sensitivity and specificity; however, doing so is much more expensive (3).

Shalev et al. treated 55 patients without complex cysts and with normal CA125 levels with operative laparoscopy and noted that all the cysts were benign, whereas among 75 patients with complex cysts and high CA125 levels that underwent laparotomy 23 had malignant lesions (11).

In conclusion, not all cysts in postmenopausal women require surgery; cysts less than 5 cm, particularly those without a solid component, in patients with normal CA125 levels may be followed up.

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