

# CLINICOPATHOLOGIC FEATURES OF PROBABLY MALIGNANT ADNEXAL MASSES WITHOUT SIGNS OF ASCITES AND CARCINOMATOSIS

## ASİT VE KARSİNOMATOZİS BULGUSU OLMAYAN YÜKSEK OLASILIKLA MALİGN ADNEXSİYEL KİTLELERİN KLİNİK VE PATOLOJİK ÖZELLİKLERİ

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**Cite this article as:** Yumru Celiksoy H, Sozen H, Baktiroglu HM, Topuz S, Salihoglu Y. Clinicopathologic features of probably malignant adnexal masses without signs of ascites and carcinomatosis. J Ist Faculty Med 2021;84(2):192-6. doi: 10.26650/IUITFD.2020.0038

### ABSTRACT

**Objective:** Our objective was to assess the patients who have probable early stage ovarian cancer.

**Material and Method:** Between 2010-2018, 208 patients with isolated adnexal masses who underwent surgery due to presumed malignancy were analyzed. We excluded patients with radiologic evidence of ascites and tumour implants.

**Results:** According to the final pathology reports, 52 (25%) of 208 patients had benign tumours, 46 (22%) were borderline, and 110 (53%) patients' tumours were malignant. The most unexpected benign tumours were serous cystadenofibroma. Of the malignant tumours, 3 were uterine sarcomas, 8 were metastatic ovarian tumours (all gastrointestinal origin), and 99 were primary ovarian cancers. Seventy-six of 99 primary ovarian cancers were epithelial and 23 were nonepithelial. The most common histologic types were respectively serous and endometrioid adenocarcinoma. Seventy-six percent of primary ovarian cancers were early stage (stage 1-2) and 24% were advanced stage (stage 3-4).

**Conclusion:** Patients with a suspicious adnexal mass, even if ascites or carcinomatosis are not existing, have a high rate of malignancy and should be managed considering this risk.

**Keywords:** Adnexal mass, ovarian cancer, malignancy

### ÖZET

**Amaç:** Amacımız muhtemelen malign adneksiyel kitlesi olan hastaları değerlendirmektir.

**Gereç ve Yöntem:** 2010-2018 yılları arasında salt adneksiyel kitlesi olan ve malignite riski nedeniyle ameliyat yapılan 208 hastanın medikal verileri incelendi. Radyolojik olarak asit ve tümöral implant bulgusu olan hastalar çalışma dışı bırakıldı.

**Bulgular:** Nihai patoloji raporlarına göre 208 hastanın 52'si (%25) benign, 46'sı (%22) borderline ve 110'u (%53) malign idi. En beklenmedik benign tümör seröz kistadenofibrom idi. Malign tümörlerin 3'ü uterin sarkom, 8'i metastatik over kanseri (tümü gastrointestinal kaynaklı), 99'u primer over kanseri idi. Doksan dokuz primer over kanserinin 76'sı epitelyal, 23'ü nonepitelyal idi. En sık görülen histolojik tipler sırasıyla, seröz ve endometrioid adenokarsinom idi. Primer over kanserlerinin %76'sı erken evrede (evre 1-2), %24'ü ileri evrede (evre 3-4) idi.

**Sonuç:** Şüpheli adneksiyel kitlesi olan hastalarda, asit veya karsinomatosis bulgusu olmasa bile, yüksek malignite riski mevcuttur ve bu risk göz önünde bulundurularak yönetilmelidir.

**Anahtar Kelimeler:** Adneksiyel kitle, over kanseri, malignite

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**Submitted/Başvuru:** 10.05.2020 • **Revision Requested/Revizyon Talebi:** 07.07.2020 •

**Last Revision Received/Son Revizyon:** 14.10.2020 • **Accepted/Kabul:** 24.11.2020 • **Published Online/Online Yayın:** 23.03.2021



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## BACKGROUND

Adnexal masses are one of the leading causes of admission to the gynecology outpatient clinic and the underlying cause could be malignancy. Ovarian cancer is a common cause of death among women; catching it in the early stage is the main issue (1). Complex adnexal masses are already considered as high-risk lesions and surgical removal is advised, but the route is important (2). Procedure and quality of primary surgery (e.g. laparotomy/laparoscopy, incision type, complete debulking, etc.) and surgeon's experience and knowledge play a major role in the prognosis of ovarian cancer. Studies have shown that consultant gynecologic oncologists (GO) improve the survival and centralization of ovarian cancer is warranted and cost-effective (3, 4). On the other hand, minimally invasive surgery (MIS) is recommended for adnexal masses presumed to be benign, but not for likely malignant tumours. MIS is suitable for patients but carries the risk of tumour cell dissemination and trocar site metastasis due to cyst rupture (5, 6). Thus, in district hospitals, gynecologists should be able to easily distinguish patients who need to be referred to tertiary hospitals with gynecologic oncology units, and GOs should make the right management and surgical plans. For this purpose, many methods have been developed; some of them are too complex to be used in daily practice, and some include markers that cannot be attained everywhere (7).

Our objective was to assess the patients with probable early-stage ovarian cancer. For this purpose, we included suspicious isolated adnexal masses and excluded patients with radiologic evidence of ascites and tumour implants.

## MATERIAL AND METHOD

After receiving approval from the ethics committee of Istanbul University, medical records of 264 patients who were referred to our gynecologic oncology clinic and underwent surgery for suspicious isolated adnexal masses between January 2010 and December 2018, were abstracted. Two hundred eight patients were included in the study because there were missing data for 56 patients. Patients aged under 18 or above 85 years, had pregnancy, had a history of malignancy, had undergone surgery for borderline ovarian tumour (BOT) or ovarian cancer and had signs of ascites, pleural effusions, bowel obstruction, omental cake or tumoural implants were excluded from the study. All patients underwent transvaginal or transrectal and transabdominal two-dimensional (2D)-USG by a GO during gynecologic evaluations. The presence of a multilocular cystic lesion, solid areas, bilateral lesions were noted. Tumour size was based on the largest diameter on USG. Serum CA125 levels were measured preoperatively using an ECLusys CA125 II assay (Roche Diagnostics, Tokyo, Japan). Patients who were

suspected of having isolated adnexal masses according to USG findings, CA125 levels, and menopausal status, underwent magnetic resonance imaging (MRI) and evaluated in our department's weekly multidisciplinary team conference. Patients with presumed malignancy were underwent laparotomy and masses were sent for frozen section analysis. According to the results of the preoperative frozen section, a surgical procedure was performed with consideration to age and fertility requirements. In some circumstances, re-staging was performed. The final histopathologic diagnosis was considered as the gold standard for defining outcomes. Tumours were classified and staged according to the World Health Organization (WHO) and International Federation of Gynecology and Obstetrics (FIGO) classifications. If the patient was amenorrheic for one year or if the patients who had undergone hysterectomy were aged 50 years or older, they were accepted as postmenopausal.

## Statistics

The Statistical Package for the Social Sciences (SPSS) 21.0 version was used for all statistical analyses. Kruskal-Wallis H analysis and the Chi-square test were used as nonparametric methods, and one-way analysis of variance (ANOVA) was used as a parametric method. P values <0.05 were considered statistically significant.

Data are expressed as mean±standard deviation (SD) or median and interquartile range (IQR). Categorical values were expressed as absolute numbers and percentages. The post hoc test was used for variables with significant differences to identify which groups had the difference.

## RESULTS

Almost all patients were symptomatic and the most common symptoms were abdominal pain and bloating. One hundred three patients were in the premenopausal period and 105 patients were in the postmenopausal period. According to the definite pathology reports, 52 (25%) of the 208 patients had benign masses, 46 (22%) had borderline tumours and 110 (53%) had malignant tumours. There was 86% compatibility between frozen section and final pathology, and the re-staging surgery rate was 4.3%. The characteristics of the patients are given in Table 1. The age and menopausal status of the prognostic factors were significantly different only in the borderline group, all other factors were similar between the groups. The most common histological subtype was serous borderline tumours in premenopausal and serous adenocarcinomas in postmenopausal period. The most unexpected benign tumours were serous cystadenofibromas among all the patients.

Three of the 110 malignant tumours were uterine sarcomas, 8 were metastatic ovarian tumours (all gastrointestinal origin), and 99 were primary ovarian cancers. Sev-

**Table 1:** Characteristics of patients

Prognostic factors	Benign (n=52)	Borderline (n=46)	Malignant (n=110)	$\chi^2$	P
Age (y)	51.5 ( $\pm$ 13.7)	41.6 ( $\pm$ 13.4)	51.9 ( $\pm$ 16.0)	F=8.32*	<0.001
BMI, kg/m <sup>2</sup>	28.1 (24-32)	26 (24-29.3)	27.3 (25-31)	3.437	0.18
Gravidity	3 (1-4)	1 (0-3)	2.5 (1-4)	4.862	0.09
Parity	2 (0.5-3)	1 (0-3)	2 (1-3)	5.555	0.06
Menopause status, n (%)					
Premenopausal	22 (42.3)	32 (69.6)	49 (44.5)	9.565	<0.05
Postmenopausal	30 (57.7)	14 (30.4)	61 (55.5)		
Tumour diameter, cm	11 (7-15)	10 (6-14)	10.5 (8-17)	2.208	0.33
Laterality, n (%)					
Unilaterally	43 (82.7)	32 (69.6)	94 (85.5)	5.470	0.07
Bilaterally	9 (17.3)	14 (30.4)	16 (14.5)		
USG findings, n (%)					
Solid	25 (17.3)	26 (8.7)	66 (11.8)	3.132	0.54
multiloculated	9 (48.1)	4 (56.5)	13 (60)		
solid+multiloculated	18 (34.6)	16 (34.8)	31 (28.2)		
CA125,U/ml	55.5 (20-204)	63 (23-213)	98 (28-261)	1.969	0.37

\* For age, one-way variance analysis is done and f value is given; BMI: Body-mass index

enty-six of the 99 primary ovarian cancers were epithelial and 23 were nonepithelial. Seventy-five of the primary ovarian cancers were early stage (stage 1-2) and 24 were advanced stage (stage 3-4); the most common types were serous (n=23) and endometrioid (n=22) adenocarcinoma, respectively. Forty-one of the 46 borderline tumours were early stage, and five were advanced stage.

Among the various histologic subtypes, serous cystadenofibromas accounted for most false-positive cases (Table 2). Bilateralism was present in 39 (19%) cases and 77% of them were borderline or malignant. Although not statistically significant, solid findings were more common in malignant cases.

**Table 2:** False-positive (benign) cases

Benign	n=52
Serous cystadenofibroma	12
Endometriosis	2
Dermoid cyst	3
Tubo-ovarian abscess	5
Fibroma/thecoma	8
Leiomyoma	7
Mucinous cystadenoma	8
Brenner tumour	2
Sex cord tumour	2
Noroendocrine tumour	2
Struma ovarii	1

## DISCUSSION

In the United States, it is estimated that there is a 5 to 10% lifetime risk for women undergoing surgery for a suspected ovarian neoplasm (8), and these are associated with a significant risk of malignancy. McDonald et al. found 48% ovarian malignancy in 272 patients with complex or solid adnexal masses (9). Advanced ovarian cancer has a 20-47% five-year survival rate, and 70-90% in the early stage (10). For the patients with early-stage ovarian cancer, comprehensive surgical staging and treatment by a consultant GO is recommended to improve survival (11, 12). Catching ovarian cancer in the early stages, would lead to better planning of treatment and more acceptable prognoses. However, it is widely recognized that ovarian malignancy is difficult to detect during its early stages.

Transvaginal USG should be the first-choice modality in patients with suspicious isolated ovarian masses (11), but is not sufficient alone. The American College of Obstetricians and Gynaecologists (ACOG) recommends referral of women with a pelvic mass to a GO if any are present; elevated CA125 levels, nodular, fixed pelvic masses, ascites, evidence of metastases or an elevated score on a formal risk assessment test such as the multivariate index assay (MIA), Risk of Malignancy Index (RMI), or the Risk of Ovarian Malignancy Algorithm (ROMA) or one of the ultrasound-based scoring systems from the International Ovarian Tumour Analysis (IOTA) group (7). The United States Food and Drug Administration (FDA) has approved the MIA and ROMA to further assess the risk

of ovarian cancer in adult women with an already identified adnexal mass (13, 14). However, human epididymis protein 4 (HE4) and other markers of MIA cannot be tested in low-resource settings. The RMI is recommended by the Royal College of Obstetricians and Gynaecologists (RCOG), who expressed that the 'RMI-1' is the most utilized, widely available, and validated effective triaging system for women with suspected ovarian cancer (15). However, its use in BOTs and early-stage ovarian cancer is limited (16, 17). MRIs identify the adnexal lesions well, and could be regarded as a reliable non-invasive modality for patients with indeterminate lesions (18).

The RCOG said that laparoscopy could be performed even in postmenopausal women if RMI <200, (10) but according to our high false negative rates, it is hazardous. Occult malignancy must always be considered. The main problems are stage I invasive diseases and surgical staging of these cases. Inadvertent rupture of a malignant mass makes it stage 1C1 and patients need to take adjuvant chemotherapy; a thorough exploration of the abdominal cavity is not enough in this situation (19, 20). On the other hand, BOTs are stage I tumours in more than 90% of cases and behave like benign tumours in almost all cases. Aggressive surgical treatment by specialized oncologic surgeons is not reasonable in these cases. Nevertheless, port-site metastasis is still an issue for BOTs (21).

In a multi-centered study, ultrasound-based rules (B and M-rules) were applied to 1066 patients with persistent adnexal masses (n=1233). These rules worked rather well for endometriomas, dermoid cysts, simple cysts and advanced invasive malignancies, but they did not work well for hydrosalpinx, peritoneal cysts, abscesses, fibromas, rare benign tumours, Stage I borderline tumours and Stage I primary invasive malignancies (22). In a meta-analysis, comparing the ability of 19 methods to pre-operatively discriminate between benign and malignant adnexal masses, the Simple Rules had a sensitivity of 93% and a specificity of 81% when classifying inconclusive tumours as malignant and were found superior to all other methods (16), but they did not isolate adnexal masses in our group of patients.

In 2016, IOTA group published a study and emphasised that despite the combination of simplicity and excellent performance, important limitations of the Simple Rules were the inconclusive results in a proportion of cases and the absence of an estimated risk of malignancy. The ability to provide accurate risk estimates is highly relevant for risk stratification and individualized patient management. They declared that type of centre also needed to be included in our risk estimation, because the risk of a malignant tumour is higher in oncology centres than in others. They found that ascites was the most predictive of

malignancy and irregular multilocular-solid tumours with a diameter of  $\geq 100$  mm were the least predictive. Type of centre had a coefficient of 0.9 (23). In our study we did not include ascites because it is known as an apparent sign of advanced-stage malignancy. We did not find any sonographic findings that were statistically different between groups, only solid images were more common in malignant cases even though not statistically significant.

In our study, the misestimation rate was %25 in adnexal masses which were presumed malignant, based on both USG and MRI findings. It had an original setting but we did not use specific risk modelling or a scoring system, its subjectivity and retrospective design was the main limitation.

This study revealed that ovarian malignancy rate was high among cases classified as suspicious isolated adnexal mass, even without ascites or carcinomatosis. We used MRI but in the low-resource settings, these masses should be characterized by USG with simple methods. For this purpose, further prospective studies need to be designed for the detection of borderline and non epithelial ovarian tumours and especially stage I ovarian cancers instead of advanced stage ovarian cancers.

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**Acknowledgement:** We would like to thank David F. Chapman for language editing of the manuscript.

**Ethics Committee Approval:** This study was approved by the Ethical Committee of the Istanbul University, Istanbul Faculty of Medicine (Date:07.05.2019-616, No:2019/538).

**Peer Review:** Externally peer-reviewed.

**Author Contributions:** Conception/Design of Study- H.Y.Ç., S.T., Y.S.; Data Acquisition- H.Y.Ç., H.M.B.; Data Analysis/Interpretation-H.S.; Drafting Manuscript- H.Y.Ç., H.M.B.; Critical Revision of Manuscript- H.S., S.T., Y.S.; Final Approval and Accountability- H.Y.Ç., H.S., H.M.B., S.T., Y.S.

**Conflict of Interest:** Authors declared no conflict of interest.

**Financial Disclosure:** Authors declared no financial support.

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**Teşekkür:** Makalenin İngilizce düzenlemeleri için David F. Chapman'a teşekkür ederiz.

**Etik Komite Onayı:** Bu çalışma için etik komite onayı İstanbul Üniversitesi, İstanbul Tıp Fakültesi Etik Kurulu'ndan alınmıştır (Tarih:07.05.2019-616, Sayı:2019/538).

**Hakem Değerlendirmesi:** Dış bağımsız.

**Yazar Katkıları:** Çalışma Konsepti/Tasarım- H.Y.Ç., S.T., Y.S.; Veri Toplama- H.Y.Ç., H.M.B.; Veri Analizi/Yorumlama- H.S.; Yazı Taslağı- H.Y.Ç., H.M.B.; İçeriğin Eleştirel İncelemesi- H.S., S.T., Y.S.; Son Onay ve Sorumluluk- H.Y.Ç., H.S., H.M.B., S.T., Y.S.

**Çıkar Çatışması:** Yazarlar çıkar çatışması beyan etmemişlerdir.

**Finansal Destek:** Yazarlar finansal destek beyan etmemişlerdir.

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