EJGO European Journal of Gynaecological Oncology

Clinical and ultrasound features of benign, borderline, and malignant invasive mucinous ovarian tumors

A. Pascual[1], S. Guerriero[2], N. Rams[3], L. Juez[4], S. Ajossa[2], B. Graupera[1], L. Hereter[1], A. Cappai[2], M. Pero[3], M. Perniciano[2], T. Errasti[4], J. Parra[3], M. Solis[4], J.L. Alcázar[4]

[1] Department of Obstetrics, Gynecology and Reproduction, Hospital Quirón Dexeus, University Autonoma of Barcelona, Barcelona (Spain)
[2] Department of Obstetrics and Gynecology, Policlinico Universitario Duilio Casula, University of Cagliari, Monserrato, Cagliari (Italy)
[3] Department of Obstetrics and Gynaecology, Santa Creu i Sant Pau Hospital, University Autonoma of Barcelona, Barcelona
[4] Department of Obstetrics and Gynecology, Clinica Universidad de Navarra, University of Navarra, Pamplona (Spain)

Summary

Objective: To compare clinical and sonographic features of benign, borderline, and malignant invasive mucinous ovarian tumors (MOTs). *Materials and Methods:* Retrospective observational multicenter study comprising 365 women (mean age: 46.1 years) with a histologically confirmed benign, borderline or malignant invasive MOT. Clinical data (patient's age, patient's complaints), tumor markers (CA-125 and CA-19.9), and sonographic data (tumor size, bilaterality, morphology –unilocular, multilocular, unilocular-solid, multilocular-solid and solid-, and IOTA color score) were reviewed and compared among these three groups. Women with ultrasound evidence on intra-abdominal disease spread were excluded. *Results:* Three hundred seventy-eight MOTs (14 women had bilateral lesions) were analyzed. Histologically, 287 tumors were benign, 51 were borderline, and 40 were malignant. No difference in patient's mean age was observed. Women with borderline or invasive tumors were less frequently asymptomatic. Tumors were larger in case of invasive lesions. Borderline and invasive tumors showed solid components and exhibited IOTA color score 3 or 4, more frequently than benign lesions ($p < 0.001$). However, the authors discovered that 16 out of 51 (31.4%) of borderline tumors and six out of 40 (15.0%) of invasive cancers had no solid components and a color score 1 or 2, and were considered as a benign lesion by the sonologist. On the other hand, 96 out of 287 (33.4%) benign mucinous cystadenoma exhibited solid components and/or a color score of 3 or 4. *Conclusions:* In spite of statistical differences, the authors observed significant overlapping in ultrasound features among benign, borderline, and invasive ovarian mucinous tumors that renders a difficult accurate preoperative discrimination among these lesions.

Key words: Ovary; Mucinous tumor; Ultrasound; Diagnosis.

Introduction

Mucinous ovarian tumors (MOT) represent a spectrum of neoplasias from benign to borderline and invasive lesions [1]. Among benign tumors, mucinous cystadenomas account for 10-15% of all cases. Whereas, borderline mucinous tumors comprise up to 67% of all ovarian borderline lesions and mucinous cystadenocarcinomas account for 2.4% of all invasive epithelial ovarian cancers [2]. Studies have shown that mucinous cystadenocarcinomas are characterized by a stepwise development from well-established precursor lesions, such as benign and borderline tumors, and that typically present at early stage, are indolent, and have a good prognosis [3, 4].

Ultrasound features of MOTs have been well described in the literature. Typically, they are described as large multilocular cysts [5, 6]. However, when analyzing data from large series assessing the role of ultrasound, using subjective assessment by expert examiners, for the specific diagnosis of ovarian tumors, it is surprising to observe that sensitivity for benign mucinous cystadenomas is low [7, 8]. The present authors wondered why is so difficult to achieve a correct ultrasound diagnosis for this particular type of ovarian lesion. Therefore, the aim of this study was to explore whether any clinical and ultrasound features could help for discriminating benign, borderline, and invasive MOTs.

Materials and Methods

This is a retrospective observational study performed at four tertiary care university hospitals. Institutional Review Board approval was obtained from each institution. Due to the retrospective study design, patient informed consent was waived.

Eligible patients were all consecutive women with histologically confirmed diagnosis of a primary mucinous ovarian tumor (benign, borderline or invasive) that underwent preoperative ultrasound characterization of the tumor from January 2001 to December 2014. Patients were identified through a database search performed at all four hospitals.

Exclusion criteria were as follows: 1) Histologic diagnosis of metastatic mucinous ovarian neoplasm (primary origin from pancreas, appendix, bowel, colon-rectum, stomach or biliary tract, pseudomyxoma peritonei), 2) incomplete clinical or ultrasound data, 3) time elapsed from ultrasound to surgery > four months, and 4) evidence on ultrasound examination of intra-abdominal spread of disease.

Revised manuscript accepted for publication January 27, 2016

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVIII, n. 3, 2017
doi: 10.12892/ejgo3560.2017

7847050 Canada Inc.
www.irog.net

All women had undergone transvaginal or transrectal ultrasound prior to surgery for ovarian tumor characterization. In cases of large tumors, transabdominal ultrasound was also performed. Several ultrasound machines available on the market were used in the different hospitals throughout the study period.

An extensive review of all clinical, ultrasound, and histologic records from all patients identified through database search was done. All principal investigators at each center (JLA, SG, MAP, and NR) had a meeting before starting data collection in order to agree which clinical and ultrasound variables should be retrieved from databases. The consensus reached determined that the minimum data available for the patient to be included should be the following: a) Clinical data – patient's age, menopausal status, patient's complaints, surgery performed within three months after diagnosis, and CA-125 and CA-19.9 serum levels were also recorded, if available. b) Ultrasound data – tumor largest size, determined as the largest diameter obtained from the measurement of tumor size in all three orthogonal planes, tumor type (unilocular, unilocular solid, multilocular, multilocular solid, solid; tumor vascularization determined as per IOTA color score [9]; presence of ascites and/or carcinomatosis (for exclusions). All ultrasound data were retrieved from original reports. No re-review of images or videoclips was performed. c) Histologic data – report must state specific diagnosis of benign, borderline or invasive mucinous ovarian tumor (this was used as a reference standard).

All ultrasound examinations had been performed or supervised by expert examiners. In many histologic reports, the distinction between intestinal-type and endocervical-type mucinous tumor [10] was lacking. Therefore, the authors decided not to analyze data according to this histological sub-classification. Borderline and invasive carcinomas were staged according to FIGO classification [11].

Categorical variables are presented as number and percentage. The Kolmogorov-Smirnov test was used to assess data distribution for continuous variables. These variables are presented as range and mean with standard deviation (SD) or median with interquartile range (IQR) depending on data distribution. Categorical variables were compared using chi-squared test. Continuous variables were compared using one-way ANOVA with Bonferroni post-hoc test or U-Mann-Whitney test for pair comparisons where appropriated.Receiver operating characteristic (ROC) curves for tumor size, CA-125 and CA-19.9 were plotted for assessing the diagnostic performance of these variables for discriminating between benign and borderline or invasive lesions. Borderline and invasive lesions were considered as one group for ROC analysis. The authors calculated sensitivity and specificity for CA-125 and CA-19.9 using a cut-off of 35 UI/ml for both tumor markers. A p value < 0.05 was considered as statistically significant for all tests. All analyses were done using the SPSS 20.0 statistical package.

Results

Database search identified 397 eligible women. Fifty-two women were excluded for non-ovarian mucinous tumor (n=7), incomplete data (n=18), evidence of intra-abdominal spread of disease (n=4) and > three months from ultrasound to surgery (n=5). Therefore, 365 women were ultimately included.

Patients' mean age was 46.1 (SD: 15.2) years, ranging from 14 to 90 years. Two hundred thirty-seven (64.9%) women were premenopausal and 128 (35.1%) were postmenopausal.

Most women were asymptomatic (n=215, 58.9%). Seventy-four (20.3%) women complained of pelvic/abdominal pain, sixty-four (17.5%) women presented with abdominal swelling, and 12 (3.3%) patients had uterine bleeding.

Table 1. — *Tumor stage distribution in borderline and invasive lesions.*

	Borderline		Invasive	
Stage	n	%	n	%
Ia	37	75.5	18	48.6
Ib	3	6.1	3	8.1
Ic	9	18.4	7	18.8
IIb	0	0	3	8.1
IIIb	0	0	1	2.7
IIIc	0	0	1	2.7
Total	49*	100	37**	100

*Three bilateral, **Four bilateral.

Fourteen (3.8%) women had bilateral mucinous tumors, giving a total number of 378 masses assessed. Histologically, 287 (75.9%) tumors were benign mucinous cysts; 51 (13.5%) lesions were borderline mucinous tumors, and 40 (10.6%) were invasive mucinous cystadenocarcinomas. Most borderline and invasive carcinomas were Stage I (Table 1).

Clinical features of benign, borderline, and invasive lesions are shown in Table 2. The authors found that patients with benign lesions were more frequently asymptomatic, with lower values for CA-125 and CA19.9, and were smaller than borderline and invasive tumors. They did not observe differences in patient's age, menopausal status, and bilaterality.

CA-125 was available for 246 cases (169 benign tumors, 40 BOTs and 37 invasive tumors). CA-19.9 was available for 119 cases (82 benign tumors, 24 borderline, and 13 invasive tumors). Sensitivity and specificity for CA-125 and CA-19.9 were 54.5% and 88.2%, and 48.6% and 92.7%, respectively. ROC curves for tumor size, CA-125, and CA-19.9 are shown in Figures 1 to 3. According to ROC analysis for CA-125 and CA-19.9, it seems that 35 UI/ml cut-off was not the best one. A better cut-off for CA-125 would be 14 UI/ml (sensitivity: 82% and specificity: 56%) and for CA-19.9 it would be 11.7 UI/ml (sensitivity: 81% and specificity: 71%).

Ultrasound features regarding tumor type and vascularization are shown in Table 3. Borderline and invasive tumors showed solid components and exhibited IOTA color score 3 or 4, more frequently than benign lesions. However, the authors discovered that 16 out of 51 (31.4%) borderline tumors and six out of 40 (15.0%) invasive cancers had no solid components and a color score 1 or 2, and were considered as a benign lesions according to the examiner's subjective impression as stated in the original report (Figures 4 and 5). On the other hand, 96 out of 287 (33.4%) benign mucinous cystadenoma exhibited solid components and/or a color score of 3 or 4 (Figure 6).

Table 2. — *Clinical features of benign, borderline, and invasive mucinous tumors.*

	Benign	Borderline	Invasive	*p* value
Patient's age (years)*	46.5 (14.8) [15-90]	44.1 (15.4) [14-77]	47.0 (17.3) [19-84]	0.612
Asymptomatic	179 (63.7%)	23 (47.9%)	13 (36.1%)	0.015 B *vs.* BOT 0.001 B *vs.* I 0.001 BOT *vs.* I
CA-125 (UI/ml)†	12.0 (13.9) 2-234.6	26.8 (44.0) 5-21811	68.6 (115.1) 5.1-3174	0.001 B *vs.* BOT 0.001 B *vs.* I 0.009 BOT *vs.* I
CA-19.9 (UI/ml)‡	6.0 (10.9) 1-184	33.1 (243.5) 1-5888	27.3 (120.2) 1-6222	0.001 B *vs.* BOT 0.001 B *vs.* I 0.959 BOT *vs.* I
Bilateral	8 (2.8%)	2 (4.2%)	4 (11.1%)	0.052
Tumor size (cm)§	7.3 (6.0) [1.5-47.0]	9.9 (10.9) [2.4-30.0]	11.5 (7.8) [2.5-53-0]	0.067 B *vs.* BOT 0.001 B *vs.* I 0.505 BOT *vs.* I
Tumor ≥ 10 cm	93 (32.4%)	25 (49.0%)	28 (70.0%)	0.015 B *vs.* BOT 0.005 B *vs.* I 0.019 BOT *vs.* I

*Mean, SD in parentheses, range in brackets.
†Median, IQR in parentheses, range in brackets. Data available from 336 women (237 B, 53 BOT and 46 I).
‡Median, IQR in parentheses, range in brackets. Data available from 175 women (124 B, 35 BOT and 16 I).
§ Median, IQR in parentheses, range in brackets.

Table 3. — *Ultrasound characteristics of benign, borderline and invasive mucinous tumors.*

	Benign	Borderline	Invasive	Total
Unilocular				
Color score 1	54 (18.8%)	2 (3.9%)	1 (2.5%)	57
Color score 2	44 (15.3%)	0 (0%)	1 (2.5%)	45
Color score 3	1 (0.3%)	0	1 (2.5%)	2
Color score 4	0	0	0	0
Multilocular				
Color score 1	27 (9.2%)	4 (7.8%)	1 (2.5%)	32
Color score 2	66 (23%)	10 (19.6%)	3 (7.5%)	79
Color score 3	32 (11.1%)	5 (9.8%)	4 (10.0%)	41
Color score 4	1 (0.3%)	1 (2.0%)	0 (0%)	2
Unilocular solid				
Color score 1	6 (2.1%)	1 (2.0%)	0 (0%)	9
Color score 2	19 (6.6%)	3 (5.9%)	2 (5.0%)	24
Color score 3	3 (1.0%)	5 (9.8%)	4 (10.0%)	12
Color score 4	0 (0%)	2 (3.9%)	1 (2.5%)	3
Multilocular solid				
Color score 1	8 (2.8%)	0 (0%)	1 (2.5%)	9
Color score 2	11 (3.8%)	3 (5.9%)	1 (2.5%)	15
Color score 3	11 (3.8%)	7 (13.7%)	5 (12.5%)	23
Color score 4	3 (1.0%)	7 (13.7%)	11 (21.0%)	21
Solid				
Color score 1	0	0	0	0
Color score 2	1 (0.3%)	1 (2.0%)	0	2
Color score 3	0	0	1 (2.5%)	1
Color score 4	0	0	3 (7.5%)	3
Total	287	51	40	378

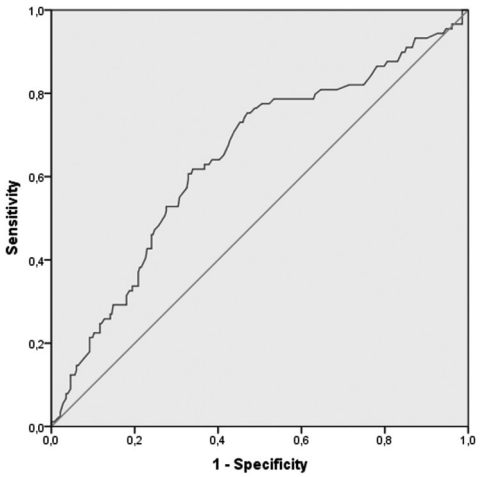

Figure 1. — ROC curve for tumor size. Area under the curve was 0.644 (95% CI: 0.577-0.711).

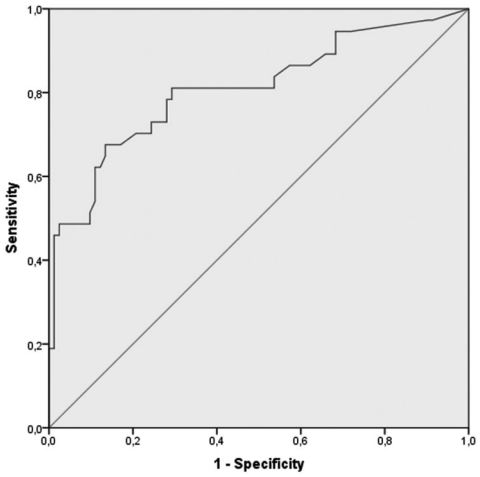

Figure 2. — ROC curve for CA-125. Area under the curve was 0.777 (95% CI: 0.721-0.843).

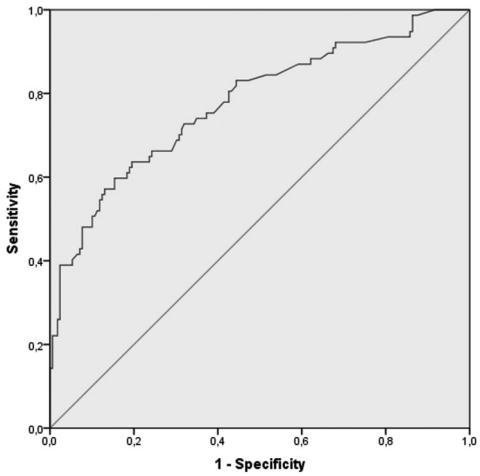

Figure 3. — ROC curve for CA-19.9. Area under the curve was 0.808 (95% CI: 0.761-0.901).

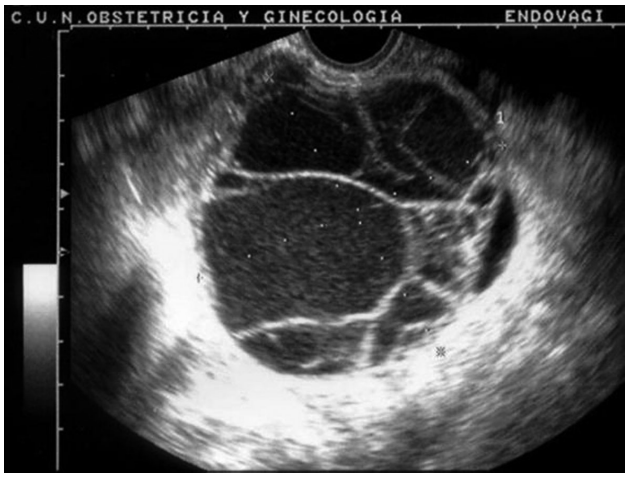

Figure 4. — Transvaginal ultrasound showing a multilocular cyst without apparent solid components. Histopathology revealed a benign mucinous ovarian tumor.

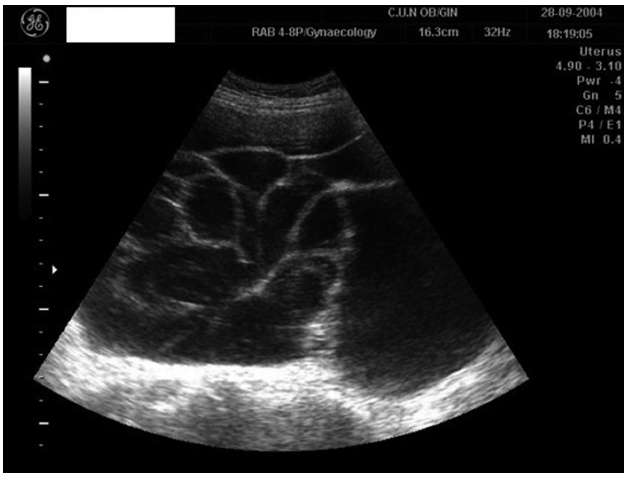

Figure 5. — Transabdominal ultrasound showing a large multilocular cyst without apparent solid components. Histopathology revealed an invasive mucinous ovarian carcinoma. Stage Ia.

Discussion

In the present study the authors evaluated some clinical and ultrasound features of benign, borderline, and invasive mucinous tumors. Although these tumors, especially benign lesions, are described as large multilocular masses [5, 6] as assessed by ultrasound, they discovered that the spectrum of findings is wide. Certainly, many of these lesions are large (38.6% of cases in our series were tumors > ten cm) and multilocular (40.7% of cases in this series). However, the presence of solid components is common, even in benign lesions (21.6% of cases in this series). Additionally, the present results show that color score assessment might be misleading, since up to 17.7% of benign tumors may exhibit moderate or abundant vascularization, but more importantly, up to 47% of borderline tumors and 25% on invasive carcinomas showed absent or scanty blood flow.

The main strengths of this study is the large series of cases analyzed and that all centers participating in the study used a same scanning protocol. However, it also has limitations. The main limitation is the retrospective design. This made it impossible to collect some ultrasound data that could be of interest, such as the number of locules, the echogenicity of the locules' content, and the size of the solid component in many cases.

The value of color score analysis should be also taken with caution in this study. The finding no flow or scanty vascularization in many masses should be considered, taking into account the large size of these masses that could explain a loss of color signals from solid areas or septa far from the transducer, due to the attenuation of the ultrasound beam. Furthermore, because of lacking data, the authors could not assess the collected variables according to different histotypes of mucinous tumors (endocervical and intestinal), what would have been interesting to do.

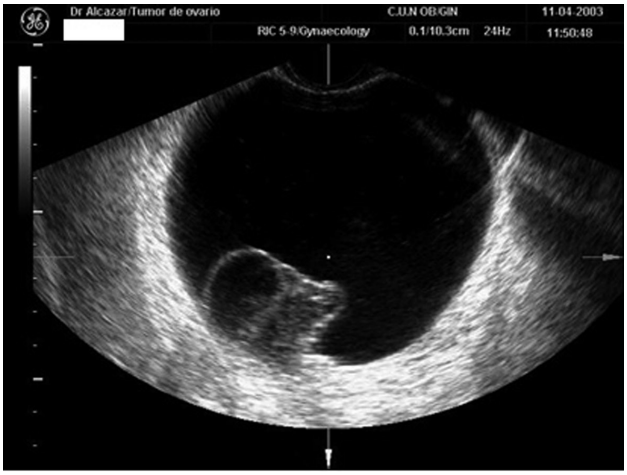

Figure 6. — Transvaginal ultrasound showing a unilocular cyst with a focal area with multiple small locules. Histopathology revealed a borderline mucinous ovarian tumor. Stage Ia.

The authors decided to exclude those cases with clear or highly suspicion of intra-abdominal spread of disease. This is an evident selection bias. However, they do think that in these cases, the suspicion of malignancy is high enough for clinical decision-making and the ultrasound features of the mass itself might be less relevant. This bias may explain why most cases of malignancy were in early stage.

Regarding the use of tumor markers for discriminating between benign and borderline or invasive tumors, the authors discovered that both CA-125 and Ca-19.9 had poor diagnostic performance. Therefore, it seems that these markers are poor predictors for malignancy, at least in ab-

sence of intra-abdominal spread.

The authors believe that the present data may be clinically relevant because of they may explain why the specific diagnosis of benign mucinous cysts is difficult. Additionally, the issue of the surgical approach for these tumors is also important. Most of these tumors are large and many of them show misleading ultrasound features, either for benign lesions, appearing as questionable or for malignant lesions appearing as benign ones. It is well known that the risk of malignancy increases in large tumors [13]. Certainly many borderline and invasive mucinous tumors are large lesions. However, benign mucinous tumors are also large masses.

Currently, laparoscopic surgery is considered the gold standard for benign adnexal masses [14]. However, the issue of tumor size is still under debate for this type of approach [15]. Some reports have shown that large masses can be surgically treated by laparoscopic surgery [16, 17]. However, the risk of intraoperative rupture and spillage is increased in large tumors [18] and, therefore, proper case selection seems to be mandatory [19]. According to the present data, this adequate selection seems to be difficult in case of mucinous tumors.

The issue of intraoperative rupture is relevant in case of mucinous lesions for two reasons: one is the risk of spreading disease. It has been shown that the prognosis of Stage I epithelial ovarian cancers worsens in case of intraoperative rupture [20]; the second one is its relationship with intra-abdominal recurrence, even in benign cystoadenomas [21], although, the latter point is under debate [22]. Taking into account the present data, it would seem reasonable to recommend women with large multilocular tumors to be referred to a gynecologic oncologist for management.

In summary, the authors have shown that although most mucinous tumors are large and multilocular the spectrum of findings is wide. Accurate discrimination between benign lesions and borderline or invasive tumors is difficult and this could have an impact on the choice of surgical approach.

References

[1] Brown J., Frumovitz M.: "Mucinous tumors of the ovary: current thoughts on diagnosis and management". *Curr. Oncol. Rep.*, 2014, *16*, 389

[2] Ledermann J.A., Luvero D., Shafer A., O'Connor D., Mangili G., Friedlander M., *et al.*: "Gynecologic Cancer InterGroup (GCIG) consensus review for mucinous ovarian carcinoma". Int. J. Gynecol. Cancer, 2014, *24*, S14.

[3] Kurman R.J., Shih IeM.: "Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm". *Hum. Pathol.*, 2011, *42*, 918.

[4] Jordan S.J., Green A.C., Whiteman D.C., Webb P.M., Australian Ovarian Cancer Study Group: "Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum?" *Gynecol. Oncol.*, 2007, *107*, 223.

[5] Guerriero S., Ajossa S., Gerada M., Virgiliioo B., Pilloni M., Galvan R., *et al.*: "Transvaginal ultrasonography in the diagnosis of extrauterine pelvic diseases". *Expert Rev. Obstet. Gynecol.*, 2008, *3*, 731.

[6] Sayasneh A., Ekechi C., Ferrara L., Kaijser J., Stalder C., Sur S., et al.: "The characteristic ultrasound features of specific types of ovarian pathology". *Int. J. Oncol.*, 2015, *46*, 445.

[7] Sokalska A., Timmerman D., Testa A.C., Van Holsbeke C., Lissoni A.A., Leone F.P., *et al.*: "Diagnostic accuracy of transvaginal ultrasound examination for assigning a specific diagnosis to adnexal masses". *Ultrasound Obstet. Gynecol.*, 2009, *34*, 462.

[8] Alcázar J.L., Guerriero S., Laparte C., Ajossa S., Ruiz-Zambrana A., Melis G.B.: "Diagnostic performance of transvaginal gray-scale ultrasound for specific diagnosis of benign ovarian cysts in relation to menopausal status". *Maturitas*, 2011, *68*, 182.

[9] Timmerman D., Valentin L., Bourne T.H., Collins W.P., Verrelst H., Vergote I.: "International Ovarian Tumor Analysis (IOTA) Group. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group". *Ultrasound Obstet. Gynecol.*, 2000, *16*, 500.

[10] Lerwill M.F., Young R.H.: "Mucinous tumours of the ovary". *Diag. Histopathol.*, 2008, *14*, 366.

[11] Prat J., FIGO Committee on Gynecologic Oncology: "Staging classification for cancer of the ovary, fallopian tube, and peritoneum". *Int. J. Gynaecol. Obstet.*, 2014, *124*, 1.

[12] Alcazar J.L., Ruiz-Perez M.L., Errasti T.: "Transvaginal color Doppler sonography in adnexal masses: which parameter performs best?" *Ultrasound Obstet. Gynecol.*, 1996, *8*, 114.

[13] Di Legge A., Testa A.C., Ameye L., Van Calster B., Lissoni A.A., Leone F.P., *et al.*: "Lesion size affects diagnostic performance of IOTA logistic regression models, IOTA simple rules and risk of malignancy index in discriminating between benign and malignant adnexal masses". *Ultrasound Obstet. Gynecol.*, 2012, *40*, 345.

[14] Canis M., Rabischong B., Houlle C., Botchorishvili R., Jardon K., Safi A., *et al.*: "Laparoscopic management of adnexal masses: a gold standard?" *Curr. Opin. Obstet. Gynecol.*, 2002, *14*, 423.

[15] Ghezzi F., Cromi A., Bergamini V., Uccella S., Siesto G., Franchi M., *et al.*: "Should adnexal mass size influence surgical approach? A series of 186 laparoscopically managed large adnexal masses". *BJOG*, 2008, *115*, 1020.

[16] Göçmen A., Atak T., Uçar M., Sanlikal F.: "Laparoscopy-assisted cystectomy for large adnexal cysts". *Arch. Gynecol. Obstet.*, 2009, *279*, 17.

[17] Scribner D.R. Jr., Lara-Torre E., Weiss P.M.: "Single-site laparoscopic management of a large adnexal mass". *JSLS*, 2013, *17*, 350.

[18] Havrilesky L.J., Peterson B.L., Dryden D.K., Soper J.T., Clarke-Pearson D.L., Berchuck A.: "Predictors of clinical outcomes in the laparoscopic management of adnexal masses". *Obstet. Gynecol.*, 2003, *102*, 243.

[19] Sagiv R., Golan A., Glezerman M.: "Laparoscopic management of extremely large ovarian cysts". *Obstet. Gynecol.*, 2005, *105*, 1319.

[20] Kim H.S., Ahn J.H., Chung H.H., Kim J.W., Park N.H., Song Y.S., *et al.*: "Impact of intraoperative rupture of the ovarian capsule on prognosis in patients with early-stage epithelial ovarian cancer: a meta-analysis". *Eur. J. Surg. Oncol.*, 2013, *39*, 279.

[21] Ben-Ami I., Smorgick N., Tovbin J., Fuchs N., Halperin R., Pansky M.: "Does intraoperative spillage of benign ovarian mucinous cystadenoma increase its recurrence rate?" *Am. J. Obstet. Gynecol.*, 2010, *202*, 142.e1.

[22] Mizrachi Y., Weiner E., Keidar R., Kerner R., Golan A., Sagiv R.: "Intraoperative rupture of benign mucinous cystadenoma does not increase its recurrence rate". *Arch. Gynecol. Obstet.*, 2015, *291*, 1135.

Corresponding Author:
J.L. ALCÁZAR, M.D., Ph.D.
Department of Obstetrics and Gynecology
Clinica Universidad de Navarra
Avenida Pio XII, 36
31008 Pamplona (Spain)
e-mail: jlalcazar@unav.es