Biparametric Magnetic Resonance Imaging as an Adjunct to CA125 and HE4 to Improve Characterization of Large Ovarian Masses

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Abstract. *Background/Aim: Aim of the present study was to assess the diagnostic value of unenhanced biparametric magnetic resonance imaging (Bp-MRI) as adjunct to CA125 and human epididymis protein 4 (HE4) in the characterization of large ovarian masses. Patients and Methods: Bp-MRI and dynamic contrast-enhanced (DCE) imaging of 53 patients with large ovarian masses were retrospectively analyzed and compared to histological diagnosis. The results of Bp-MRI and DCE were assessed by two readers in consensus for each technique individually compared to each other and then with HE4 and CA125. Results: Sensitivity, specificity, negative predictive values and positive predictive values for Bp-MRI and DCE were 92.3%, 91.4%, 94.1%, 88.9% and 84.6%, 94.3%, 89.2%, 91.7%, respectively. Both Bp-MRI and DCE were significant predictors of outcome. Among biomarkers, HE4 was significant. Considering the area under receiver operating characteristic curve the model including Bp-MRI and HE4 was not significantly different from the model including DCE and HE4. Conclusion: Bp-MRI in addition to HE4, especially in women of pre-menopausal age, could improve the characterization of large ovarian masses.*

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Large (>5 cm in diameter) pelvic masses in female patients often occur in routine clinical practice (1). Many masses in the female pelvis arise from the reproductive organs; out of these, many are ovarian tumors, both benign and malignant, which can manifest as large pelvic masses. Determining the site of origin (*e.g.* uterus, cervix, adnexa, rectum, bladder, pelvic muscles) of large pelvic masses and differentiating between tumors is essential in order to establish adequate therapeutic planning and to address a malignant mass at the appropriate Cancer Center.

Ultrasound (US) with color Doppler is the method of choice for characterization of ovarian masses (2). However, US is not able to determine the origin of a large mass (ovary, uterus or another pelvic structure) (3-6) and in up to 8% of adnexal masses, the origin remains indeterminate (3). In these patients, use of another imaging technique is mandatory (5).

Magnetic resonance imaging (MRI) represents the most useful method for determining the site of origin of larger masses, characterizing indeterminate adnexal mass at US and providing examination of the abdomen for metastases (6, 7); its use is recommended to address the final decision of conservative or surgical treatment of an adnexal mass (8).

Recently, multiparametric MRI (Mp-MRI) has emerged as an anatomical and functional imaging method that offers diagnostic accuracy in determining the origin and nature of ovarian masses (9). This includes T2-weighted (T2-W) and diffusion-weighted (DWI), as well as dynamic contrast-enhanced (DCE) MRI, and in some cases, MR spectroscopy. However, Mp-MRI is expensive and the time required to complete the study includes the use of gadolinium-based contrast agents, requiring for intravenous access.

In addition, the low specificity of CA125 for diagnosis of ovarian malignant tumor (10) should be considered. To overcome these limitations and to increase the accuracy of MRI in the characterization of ovarian masses, a limited Mp-MRI study incorporating only non-contrast morphological and DWI series could be suggested that could potentially reduce cost and time required by adding novel markers such as human epididymis protein 4 (HE4).

Our aim was to investigate the diagnostic role of biparametric morphologic T1-W, T2-W and DWI MRI (Bp-MRI) as an adjunct to CA125 and HE4 biomarkers for characterization of large ovarian lesions.

Materials and Methods

Patients. A formal approval to the Institutional Ethics Committee was not required for this retrospective observational study. All included patients gave their written informed consent for the use for research purposes of their MRI data.

We retrospectively analyzed the MRI examinations of the pelvis of 74 consecutive patients with large pelvic masses performed from January 2011 to December 2013. All patients, 12 of which with pelvic pain, underwent Mp-MRI prior to surgery to determine both the nature and origin (ovarian, uterine or other pelvic structures) of the large masses (range=5.1-18.6 cm, mean=12.5 cm), which were not established by US.

A total of 21 patients with previous pelvic surgery, current pregnancy, contraindication to receive gadolinium diethylene-triamine penta-acetic acid or glomerular filtration rate <60 ml/min/1.73 m^2, uterine leyomioma and degenerative leiomyoma or lost at follow-up, were excluded from the study.

Finally, 27 patients of pre-menopausal age (mean age=33 years) and 26 of postmenopausal age (mean age=65 years) with 61 (unilateral n=45, and bilateral n=8) ovarian masses were included in the study.

Serum samples were collected from patients before surgical intervention in a red-top vacutainer following a standard protocol. Samples were clotted for 60-90 min, then centrifuged for 10 min at 1,300 × *g*. The serum fractions were aliquoted and stored at −80˚C until analysis.

CA125 levels were evaluated by a one-step sandwich radioimmunoassay (Radim, the Netherlands). Normal levels of CA125 were considered to be less than 35 U/ml.

HE4 levels were determined using the HE4 EIA assay (Fujirebio Diagnostics, Malvern, PA, USA). According to the manufacturer's indications, normal values of HE4 were considered to be less than 150 pmol/l. According to previous studies and the manufacturer's indication,we considered normal levels to be under a threshold value of 120 pmol/l in postmenopausal women and 80 pmol/l in premenopausal women.

MRI examination. Patients underwent a standard MRI examination of the female pelvis on a 1.5 Tesla instrument (Siemens Magnetom Avanto, Erlangen, Germany), with the use of a phased-array multichannel (32 channels) body coil.

An intravenous injection of 20 mg of butyl-scopolamine (Buscopan; Boehringer Ingelheim, Italia S.p.A.) was administered to all patients to relax the bowel wall and reduce peristalstic bowel movement before MRI examinations; patients were asked to ensure a 3-hour fasting period before the MRI examination.

The MRI protocol included: T2-W half Fourier single-shot turbo spin-echo (HASTE) (slice thickness (SL)=6 mm; repetition time (TR)=1000 ms; echo time (TE)=85 ms; flip angle (FA)=150); T2-W turbo spin-echo high-resolution sequences (SL=3.00 mm; TR =3659-5740 ms; TE=95-110 ms; FA=40-150; field of view (FOV)=240×240; Matrix=256×224); T1-W flash 2D sequences (fast low-angle single-shot gradient-echo with and without fat saturation (SL=5.5 mm; TR=137-240 ms; TE=5 ms; FA 70; matrix=256×205; FOV=350×350); 3D T1-W fat-saturated gradient-echo sequences (SL=4 mm; FA=12; FOV=280×280; Matrix=256×224; TR=4 ms; TE=2 ms) in a dynamic protocol acquiring a pre-contrast scan followed by a post-contrast series of six consecutive phases of 20 s each, obtained immediately after injection of gadobenate dimeglumine (Multihance Bracco, Italy), at a dose of 0.1 mmol/kg of body weight (maximum, 20 ml), followed by injection of 20 ml of normal saline flushing the tube; axial DWI sequences (SL=4 mm, number of excitations=3, FA=90; FOV=400×400; Matrix=192×192; TR=5700 ms; TE=80 ms, b values of 0, 500 and 1000 s/mm^2 with acquisition time of 2.30 min.

We completed the study with the re-elaboration of pre- and post-contrast sequences in order to obtain subtracted images.

MRI analysis. MR images were analyzed on an LMD Sony 2451-MD monitor (resolution of 1220×1920 pixels) in consensus by two radiologists (L.M. and M.S. each with almost 20 years of experience in MRI for gynecological pathologies), who were blinded to histological findings. Two sets of hard-copy images were reviewed in consensus for each patient for Bp-MRI (T1-W, T2-W and DWI) and DCE alone. Each set was reviewed with the cases in random order on separate occasions with an interval of at least 2 weeks between each set so as to minimize observer bias. The observers recorded the location and nature (benign or malignant) of all lesions. Because our aim was to assess the diagnostic value of Bp-MRI in combination with biomarkers in the characterization of large ovarian masses, other findings (such as ascites, peritoneal and omental deposits, pelvic or para-aortic lymph nodes, and involvement of other pelvic organs) were not considered.

Analysis and interpretation of Bp-MRI: Lesion that showed T2-W dark spot sign (11), and corresponding hypointense signal on b 0 and 1,000 s/mm^2, and apparent diffusion coefficient (ADC) map, were considered benign (fibrotecoma, endometrioma *etc*.); T2-W was also used to precisely localize the signal alteration revealed on DWI. Lesions hyperintense on T1-W sequences were evaluated by T1-W fat-suppression. DWI at b values of 0.500 and 1,000 s/mm^2 were analyzed qualitatively, referring to the signal intensity of ovarian lesions, for the presence of areas with higher signal intensity than the serous fluid (urine in the bladder or cerebrospinal fluid). Lesions that showed low signal intensity on DWI obtained at b=1,000 s/mm^2 and high signal in the corresponding ADC maps were considered benign. Lesions that no showed T2-W dark spot sign and that showed high signal intensity on DWI obtained at b=1,000 s/mm^2 with lowering of the signal in the corresponding ADC maps were considered malignant. Then a quantitative analysis on the ADC map was made. A circular region-of-interest (ROI), with diameters ranging between 20 and 40 mm^2, was manually drawn within solid ovarian component showing restriction on DWI. At least three measurements were obtained and an averaged ADC value was acquired.

Analysis and interpretation of DCE-MRI: dynamic data were analyzed in consensus at a workstation. The entire adnexal mass is included in the series of six consecutive phases of 20 s after gadolinium injection. An ROI was manually drawn over the most avidly enhancing solid component, thick enhanced wall or septations of the lesion. Signal intensity (SI)–time curve was drawn. From the maximum relative enhancement and the time peak of the curve, it was determined whether there was early uptake (within the first 60 s) or not and if the maximum relative enhancement was more than 85% (with malignant tissue) or less. Lesions that showed greater enhancement during the early phase of enhancement were considered malignant, while lesions that showed initial rapid enhancement followed by a plateau were highly suspicious of malignancy, while a gradual increase in enhancement without a well-defined peak were considered benign (12).

For HE4, according to previous experience and the manufacturer's indication, we considered normal levels to be those under a threshold value of 120 pmol/l in postmenopausal women and 80 pmol/l in premenopausal women. Normal levels of CA125 were considered to be less than 35 U/ml.

Histopathological examinations of the specimen after laparoscopy were obtained: cystectomy or salpingo-oophorectomy for 27 benign lesions: three tubo-ovarian abscess, 10 teratomas (ruptured teratoma, n=2; teratoma associated with endometriomas, n=2;and six teratomas of which two were bilateral), six mutinous cystoadenomas, four ovarian fibromas, two endometriomas and two ovarian torsions; and laparotomic staging and treatment after a diagnostic laparoscopy for eight borderline tumors (serous epithelial tumors, n=2; mucinous epithelial tumors, n=4;and endometroid tumor, n=2) and 26 malignant tumors (mucinous epithelial tumors, n=4; serous epithelial tumors, n=6; Leydig cell neoplasm, n=1; endometroid tumours, n=2; bilateral metastasis, n=12; and dysmerginoma n=1).

Statistical analysis. All analyses were performed using Stata software (Stata Corp. 2013. Stata Statistical Software: Release 13;Stata Corp LP. College Station, TX, USA). Histology served as the reference standard for assessment benign and malignant ovarian masses. The results of Bp-MRI and DCE were assessed for each technique individually, and then compared to each other and then with the two markers HE4 and CA125. Sensitivity and specificity, positive predictive value and negative predictive value were calculated (with 95% confidence intervals). The McNemar test for paired binary response data was used to compare test performance. A p-value of less than 0.05 was considered statistically significant. As a simple summary measure of test performance, equivalent to the receiver operating characteristic (ROC) curve for binary tests, we calculated the average of test sensitivity and specificity. Nonparametric ROC curves were also calculated for CA125 and HE4 levels.

Logistic regression was used to investigate the independent role of diagnostic tests. A backward stepwise procedure was used to select variables retained in the final model (p=0.15). ROC curves for the logistic regression models were compared using a non-parametric test (13).

Results

Bp-MRI revealed a total of 32 true-negative lesions (Figure 1), 3 false-positives (one each of abscess, atypical teratoma and mucinous epithelial cystoadenoma) (Figure 2), 2 false-negatives (one Leydig Sertoli and 1 serous epithelial cystoadenocarcinoma) (Figure 3), and 24 true-positives (Figure 4).

Sensitivity, specificity, NPV and PPV were 92.3%, 91.4%, 94,1% and 88.9%, respectively. The mean (±SD) ADC value for benign lesions was $1{,}54\times10^{-3}\pm0.28$ mm^2/s, and for malignant ones was $0.9\times10^{-3}\pm0.25$ SD mm^2/s. An ADC value of 1.1×10^{-3} mm^2/s or more may be an optimal cut-off value for differentiating benign from malignant ovarian masses.

DCE revealed a total of 33 true-negatives, two false positives (one borderline epithelial tumor, and one mucinous epithelial cystoadenoma), 24 true-positives and 4 false-negative lesions (one Leydig Sertoli and three mucinous epithelial cystoadenocarcinomas). Sensitivity, specificity, negative predictive value and positive predictive value were and 84.6%, 94.3%, 89.2% and 91.7%.

The results of McNemar test and area under the ROC-curve (AUC) for Bp-MRI and DCE are reported in Figures 5 and 6. An AUC of 0.919 and 0.895 was revealed for B-MRI and DCE, respectively. The results of McNemar test and ROC-AUC analysis demonstrated a substantially similar accuracy of Bp-MRI compared to DCE in the differentiation between benign and malignant ovarian masses. No significant difference was revealed comparing our results for both the relationship between the percentage of true-positives (p=0.3) and false-positives (p=0.6)

In pre-menopausal patients (13 out of 53), HE4 levels (normal level=80 pmol/l) were normal in 12 out of 13 patients (benign, n=1; borderline, n=2; and benign tumor, n=9) and elevated in a borderline tumor (n=1). In post-menopausal patients (40 out of 53), HE4 levels (normal level=120 pmol/l) were normal in 28 out of 40 patients (benign, n=15; borderline, n=4; and malignant, n=9) and elevated in 12 out 40 patients (benign, n=1; borderline, n=1 and malignant, n=10 tumors). Quantitative results of HE4 levels in women of pre- and post-menopausal age are shown in Figure 7.

In pre-menopausal patients (13 out of 53), CA125 was under the threshold value (35 U/ml) in 4 out of 13 patients (benign, n=3; and borderline, n=1), and elevated in nine out of 13 patients (benign, n=6; borderline, n=2; and malignant, n=1). In post-menopausal patients (40 out of 53), CA125 levels (normal=35 U/ml) were normal in 17 out of 40 patients (benign, n=9; borderline, n=4 and malignant, n=4) and elevated 23 out of 40 patients (benign,n=7; borderline,n=1 and malignant, n=15). Quantitative results of CA125 levels in pre- and post-menopausal age are shown in Figure 8.

The ROC-AUC was determined for levels of individual serum markers for differentiating benign from malignant cases. Analysis of ROC-AUC, revealed that HE4 had the highest AUC of 0.89 (95% CI=0.88-0.91) (Figure 9) compared to CA125 (AUC=0.70,95%CI=0.65-0.80) (Figure 10).

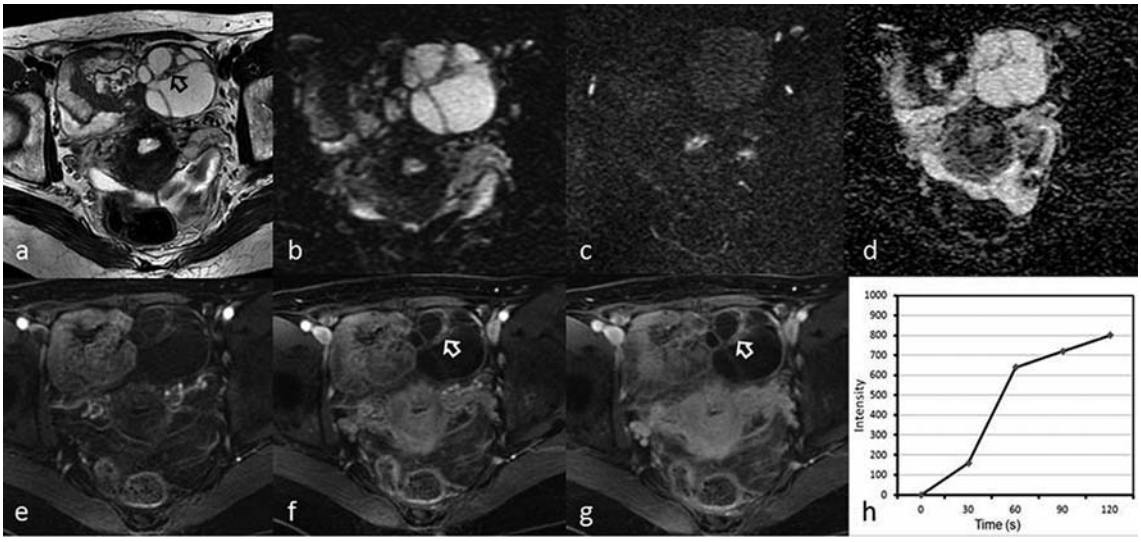

Figure 1. *Imaging of a 41-year-old woman affected by mucinous epithelial cystoadenoma (true-negative). a: Axial T2-weighted image showing a multilocular cyst on the left ovary with hypointense solid component. b,c: Axial diffusion-weighted image does not show the presence of a high signal on b-values of 0 and 1000 s/mm^2 with the apparent diffusion coefficient (ADC) map (d) giving an ADC value of 1.5×10^{-3} mm^2/s. e-g: Axial T1-weighted fat-suppressed images showing progressive enhancement in the early phases (e and f) after administration of gadobenate dimeglumine without wash-out in the late phase (g). h: Time–intensity curve obtained on the solid intracystic component.*

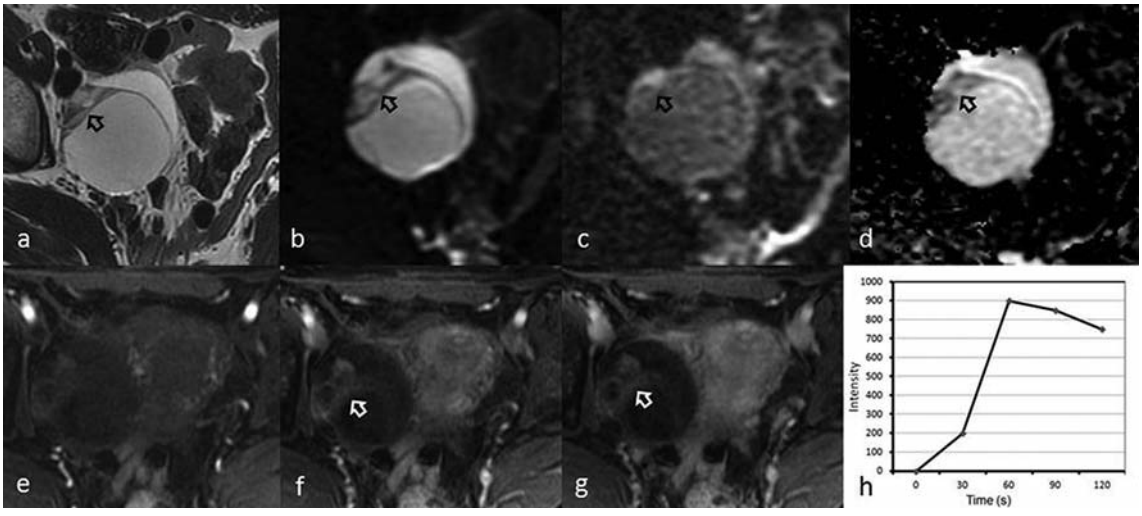

Figure 2. *Imaging of a 45-year-old woman affected by histologically proven mucinous epithelial cystoadenoma (false-positive). a: Axial T2-weighted image showing a right ovarian cyst with hypointense heterogeneous solid component (arrow). b,c: Axial diffusion-weighted image showing the presence of a heterogeneous high signal and isointensity of the solid component (arrow in b and c) on b-values of 0 and 1000s/mm^2 with apparent diffusion coefficient (ADC) map (d) giving isointensity of solid component (arrow in d) and an ADC value of 1.1×10^{-3} mm^2/s. e-g: Axial T1-weighted fat-suppressed images showing enhancement of the solid component in the early phases (arrow in f) after administration of gadobenate dimeglumine and wash-out in the late phase (arrow in g).h: Time–intensity curve obtained on the solid part of the lesion.*

In multivariate analyses, both Bp-MRI and DCE were significant predictors of outcome. Among biomarkers, HE4 was significant. CA125 was not a significant predictor of outcome and was not included in the final models. A comparison between ROC curves from logistic regression models for the combination of Bp-MRI and HE4 (AUC=0.92) and DWI and HE4 (AUC=0.95) is shown in Figure 11.

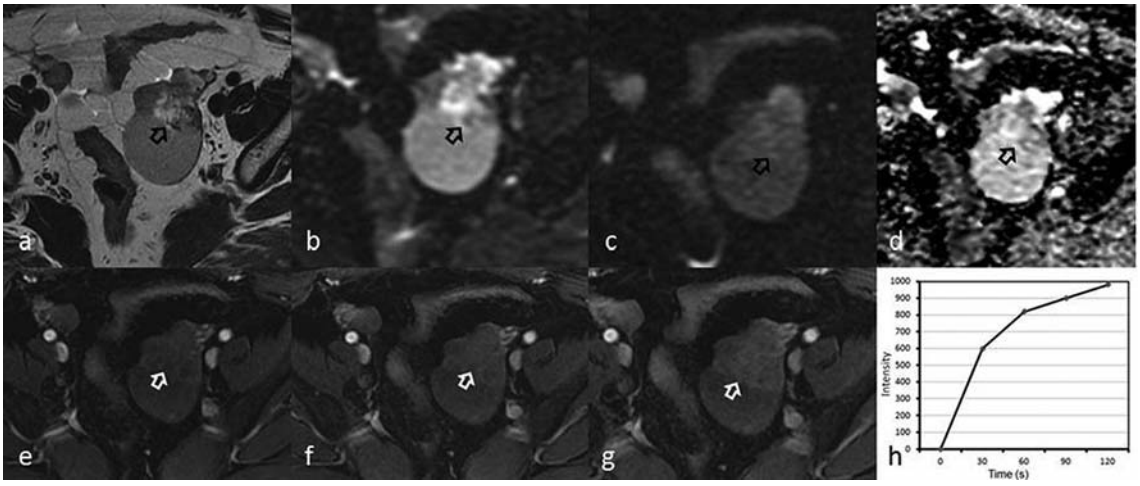

Figure 3. *Imaging of a 54-year-old woman affected by malignant Leydig-Sertoli cell tumor (false-negative). a: Axial T2-weighted image showing a hypointense cyst of the left ovary with heterogeneous solid component (arrow). b,c: Axial diffusion-weighted image does not show the presence of high signal of the solid component (arrow in b and c) on b-values of 0 and 1000s/mm^2 with an apparent diffusion coefficient (ADC) map (d) giving isointensity of solid component (arrow in d) and an ADC value of 1.38×10^{-3} mm^2/s. e-g: Axial T1-weighted fat-suppressed images showing slight hyperintensity of the solid component (arrow in e) and its progressive enhancement in the early phase (arrow in f) after administration of gadobenate dimeglumine without wash-out in the late phase (g). h: Time–intensity curve obtained on the solid part of the lesion.*

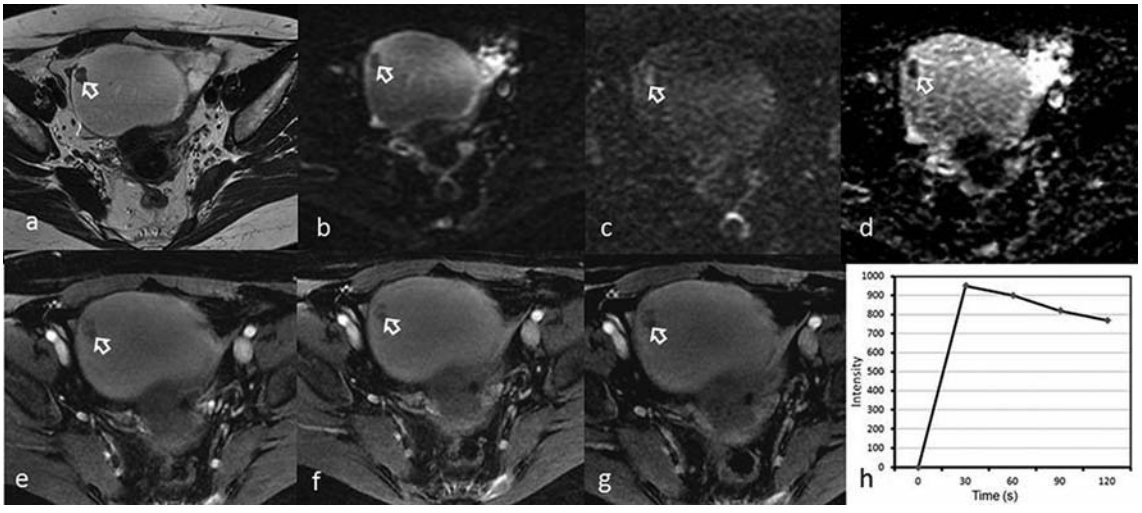

Figure 4. *Imaging of a 47-year-old woman affected by ovarian clear cell carcinoma (true-positve). a: Axial T2-weighted image showing a unilocular cyst of the left ovary with small hypointense solid component (arrow). b,c: Axial diffusion-weighted image shows the presence of low signal on b-values of 0 s/mm^2 (arrow in b) and high signal on b-values of 1000 s/mm^2 (arrow in c) with an apparent diffusion coefficient (ADC) map (d) giving hypointensity of solid component (arrow in d) and an ADC value of 0.9×10^{-3} mm^2/s. e-g: Axial T1-weighted fat-suppressed sequences showing hypointnese signal on unenhanced images (arrow in e) and enhancement in the early phases (arrow in f) after administration of gadobenate dimeglumine with wash-out in the late phase (arrow in g). h: Time–intensity curve obtained on the solid part of the lesion.*

In terms of ROC-AUC, the model including B-MRI and HE4 (AUC=0.92, 95% CI=0.85-0.99) was not significantly different from that including DCE and HE4 (AUC=0.95, 95% CI=0.90-1.00) (p=0.45).

Discussion

In the setting of pelvic masses larger than 5 cm in maximum diameter in females, for an appropriate treatment it is

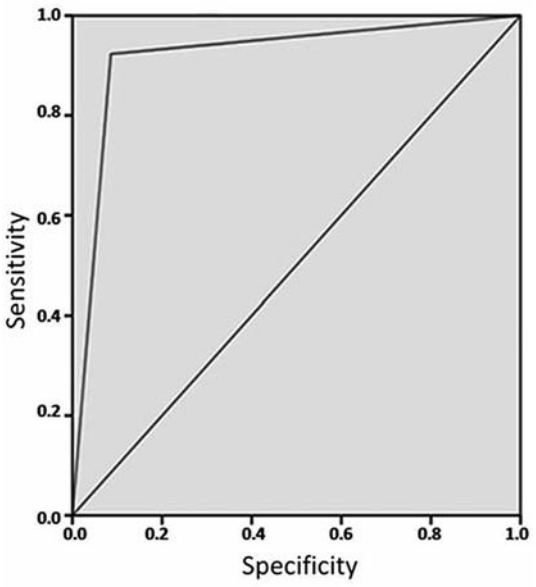

Figure 5. *Receiver operating characteristic (ROC) curve for characterization of benign and malignant adnexal masses on biparametric magnetic resonance imaging.*

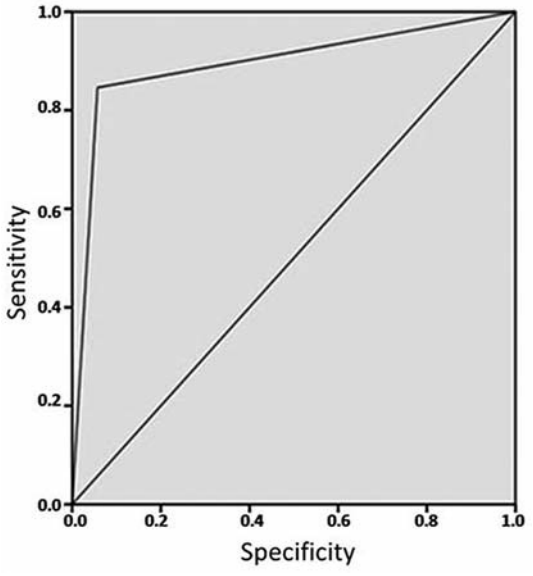

Figure 6. *Receiver operating characteristic curve for characterization of benign and malignant adnexal masses on dynamic contrast-enhanced imaging.*

essential to establish the site of origin and the nature (benign or malignant) of the lesion. US, either with transvaginal approach or a trans-abdominal one, represents the first imaging modality approach to a pelvic mass (2). US has an high sensitivity (85-100%) and poor specificity (56-60%), which may be increased by the integration of US color-Doppler evaluation (14, 15). The use of US in the evaluation of large pelvic masses in females is limited by its inability to determine the origin (ovary, uterus or another pelvic structure) and benign or malignant nature of the lesion. Some authors proposed the combined use of HE4 and CA125 levels, or HE4 for the discrimination of ovarian malignancies and for the evaluation of disease extension in epithelial ovarian carcinoma (16-18).

Mp-MRI represents a useful method that offers diagnostic accuracy in determination the origin and nature of ovarian masses (9). In order to differentiate benign from malignant masses, to overcome extensive scan time and costs, and to avoid injection of contrast material, some authors proposed a limited Mp-MRI study incorporating only non-contrast T2-W and DWI sequences (19). On the other hand, others concluded that DWI is helpful in differentiation between benign and malignant ovarian lesions (19), but a post-contrast study cannot be replaced as it helps in the decision of vascularity and integrity of the lesions.

Our aim was to assess the diagnostic value of Bp-MRI and non-contrast T1-W, T2-W and DWI sequences as an adjunct to HE4 and CA125 biomarkers for characterization of large ovarian masses. Although our series included large ovarian masses, the results are comparable to those achieved by others (21-24).

The sensitivity and specificity for DCE in the characterization of ovarian masses in the literature was 60-93.7% and 88-91% respectively (22, 23), matching our results demonstrating a sensitivity of 84.6% and specificity of 94.3%. For 61 lesions, DCE revealed a total of 33 true-negatives, two false-positives, four false-negatives and 24 true-positive lesions. For the false-positive cases, DCE showed a greater enhancement during the early phase of enhancement for both tumors. For the false-negative cases, DCE showed a gradual increase in enhancement without a well-defined peak for the Leydig Sertoli tumor. Mucinous cystoadenocarcinomas were under-estimated as borderline ovarian tumors showing moderate initial enhancement followed by a plateau.

Addition of DWI to conventional raises the specificity, positive predictive values, negative predictive values and accuracy from 58%, 66, 87% and 73% to 75%, 78%, 100% and 86%, respectively (21). Because of their distinctive histopathological characteristics (hemosiderin within endometriomas and of the keratinoid substance within mature cystic teratomas), endometriomas and mature cystic teratomas can display features on DWI overlapping with those of malignant lesions, but the morphological features and the signal intensity on T1-W with and without fat saturation and T2-W sequences show a typical finding for these diagnoses (24-28).

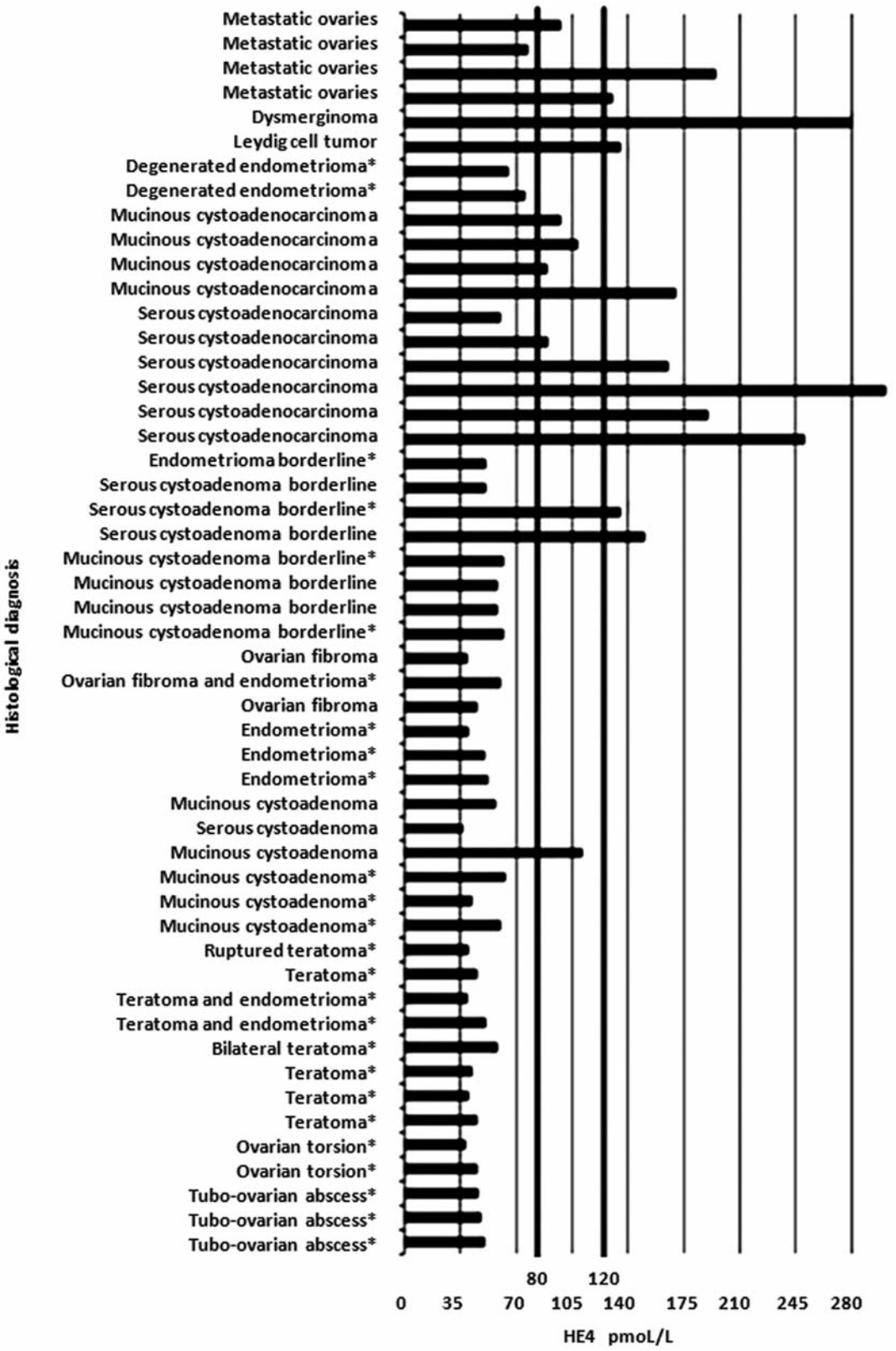

Figure 7. *Serum human epididymis protein 4 (HE4) values according to histological diagnosis for individual patients. The vertical black lines corresponds to the threshold values: 80 pmol/l in premenopausal and 120 pmol/l in postmenopausal women. *Premenopausal women.*

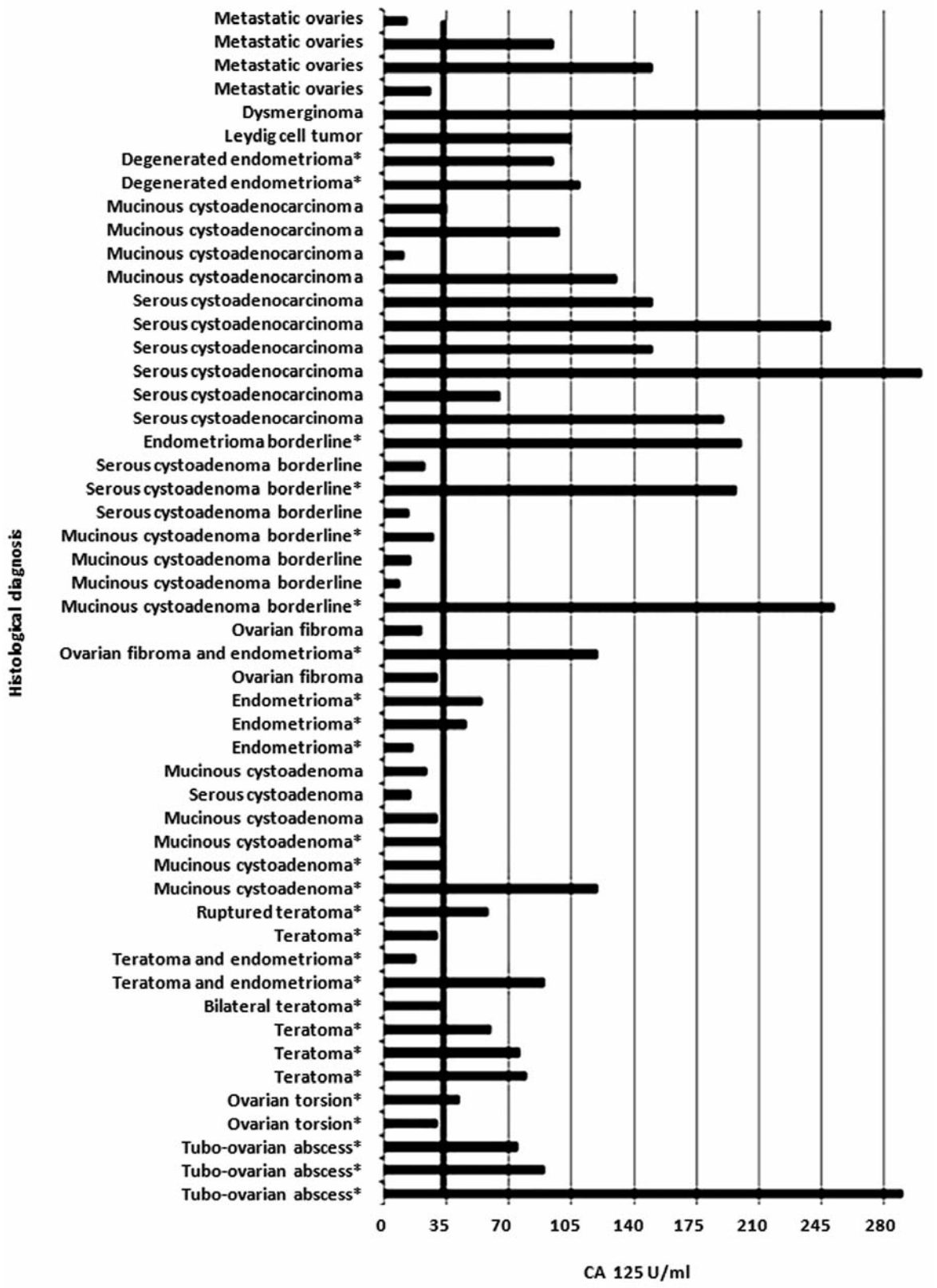

Figure 8. *Serum cancer antigen 125 (CA125) values according to the histological diagnosis. The vertical red line corresponds to the threshold value of 35 U/ml. *Premenopausal women.*

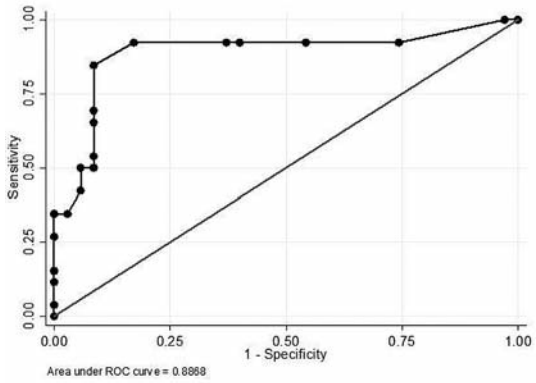

Figure 9. *Human epididymis protein 4 receiver operating characteristic (ROC) curve for differentiation of benign from malignant adnexal masses.*

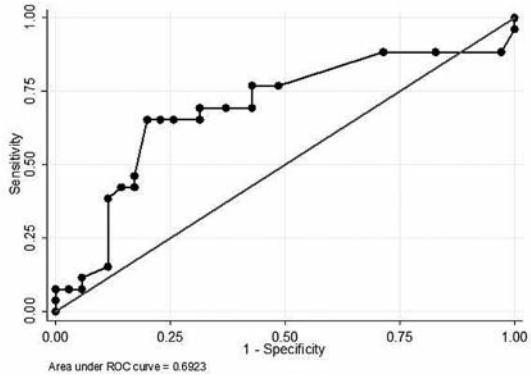

Figure 10. *Cancer antigen 125 receiver operating characteristic (ROC) area for differentiation of benign from malignant adnexal masses.*

Our results by DWI added to morphological sequences demonstrated a relatively higher sensitivity (92.3%) and specificity (91.4%) compared to the literature (21). Compared to DCE in our study, Bp-MRI demonstrated a relatively high sensitivity (92.3% *vs*. 84.6%) and low specificity (91.4% *vs*. 94.3%). In false-positive cases by Bp-MRI, DWI showed restriction, while in two false-negative cases it showed no restriction of the diffusion of water molecules. In our study, the sensitivity and specificity of Bp-MRI was relatively higher than that of DCE.

Mean ADC values for benign and malignant lesions were lower in comparison to those reported by Li *et al*. (1.54×10^{-e} ±0.28 SD mm^2/s *vs*. $1.69\times10^{-1} \pm 0.25\times10^{-\pm}$ mm^2/s, and $0.9\times10^{-s} \pm 0.25$ SD mm^2/s *vs*. $1.03\times10^{-1}\pm0.22\times10^{-\pm}$ mm^2/s, respectively). Similarly, the optimal ADC cut-off value for differentiating benign and malignant ovarian masses was lower (1×10^{-3} mm^2/s *vs*. $1.25\times10^{-1.2}$ mm^2/s) (21).

CA125 is the most widely used serum biomarker among patients with ovarian cancer. Using a cut-off level of 35 U/ml, CA125 had a sensitivity of 73.2% and a specificity of 79.2% (29-31). HE4 has the highest sensitivity and specificity as a single marker, with 82.9% sensitivity and 87.5% specificity compared to CA125 (30, 32). The accuracy in the diagnosis of ovarian malignant lesions can further potentially improve by use of both CA125 and HE4 (30), and the fact that HE4 is strictly correlated to malignant lesions (33-37).

With respect to biomarkers, our study was not comparable with those reported in the literature because our series included large ovarian benign and malignant non-neoplastic and neoplastic large ovarian masses in pre- and postmenopausal patients.

Our results demonstrate both Bp-MRI and DCE were significant predictors of outcome. Among biomarkers, HE4 was significant. CA125 was not a significant predictor of outcome and was not included in the final models. The models including DCE and Bp-MRI in addition to HE4, showed similar discriminatory ability. Despite the low specificity of CA125 levels in women of pre-menopausal age, there was a good correlation between CA125 level and inflammatory diseases and endometriosis. Normal HE4 levels indicate benign cases, while elevated HE4 levels associated with MRI findings suggestive of malignancy should indicate metastatic ovarian lesions or neoplasm of non-epithelial origin.

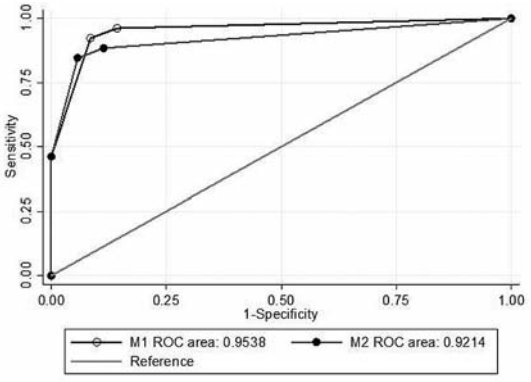

Figure 11. *Comparison between receiver operating characteristic (ROC) curves from logistic regression models for the combination of dynamic contrast-enhanced with human epididymis protein 4 (HE4) (M1) and biparametric magnetic resonance imaging with HE4 (M2).*

Our study has certain limitations. Firstly, this was a retrospective study in which two radiologists interpreted images as readers, they came to a single decision so all findings are based on a single data point. Secondly, the

study included no measurement of inter-reader variability and an inhomogeneous sample of patients, of both pre-menopausal and post-menopausal age, that may affect the biomarker levels. Thirdly, a limited number of epithelial tumors and malignant tumors (*e.g.* dysmerginoma and Leydig Sertoli) did not allow the role of Bp-MRI or DCE MRI to be established for these lesions. Finally, there was also a selection bias as only surgically operated masses were included.

In conclusion, using unhenanced Bp-MRI (saving the contrast costs) in addition to HE4 gave similar diagnostic results those of DCE, especially in premenopausal women,and could improve the characterization of large ovarian masses. According to the literature (6), we recommend adding DCE when Bp-MRI is inconclusive.

Further studies, including a larger number of patients, are required to evaluate Bp-MRI in addition to CA15 and HE4 as an alternative to Mp-MRI in differentiating benign from malignant ovarian masses.

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