Sonographic and Doppler predictors of malignancy in ovarian lesions

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Abstract

Background: To determine the best sonographic (US) and/or Doppler features that the radiologist can use as predictors or risk factors for ovarian malignancy.

Results: Among the examined 156 ovarian lesions, there were 53 malignant and 103 benign lesions. Most of the malignant ovarian lesions were noted in older age than in benign lesions p < 0.001. Majority of the malignant lesions had non-hyperechoic solid component (92.5%); it had the highest sensitivity of 92.5%, specificity of 97%, accuracy of 94.8%, positive predictive value of 94%, negative predictive value of 96%, and AUC of 0.94 in discrimination between benign and malignant ovarian lesions. The presence of papillary projection, the absence of wall definitions and thick wall, and thick septation were noted in 83%, 81%, and 53.8% of the malignant ovarian lesions respectively. Color flow Doppler shows neovascularity in 88.7% of the malignant lesions, 73.6% of them has central blood flow. The multivariate regression analysis revealed that the presence of non-hyperechoic solid component, new vascularity with central location of the blood flow, papillary projection, thick septa, and old age were the most significant parameters in predicting ovarian cancer in decreasing order of frequency according to their odds ratio (19.45, 7.55, 4.56, 3.45, and 1.45, respectively).

Conclusions: The non-hyperechoic solid component, new vascularity with central location of the blood flow, papillary projection, and thick septa were the most significant and consistent US and Doppler predictors of ovarian malignancy in addition to one clinical feature which is the old age ≥ 52 years.

Keywords: Ovarian mass, Gray-scale US, Doppler, Malignancy, Predictors
this technique may be useful as a second step technique or when the US features are inconclusive [11], while others concluded that it adds little additional information [12].

This study aims to determine the best sonographic and/or Doppler features that the radiologist can use as predictors or risk factors for ovarian malignancy, which in turn help the radiologist to select the high risk ovarian lesions that need further investigations in a specialized center.

Methods

Patients selection

This prospective cross-sectional study was approved by our institutional review board (IRB no. 17100016). Written informed consent was obtained from each patient for participation and publication after receiving information about the details of the study. This trial was registered in the US National library of medicine with NCT03175991 number in clinical trial. The sample size was calculated using the Open Epi software program, version 23.1.

This study was carried out between March 2017 and August 2018. One hundred sixteen women were studied in our center based on suspicion of having ovarian lesion on clinical examination, accidentally discovered ovarian lesion on US examination or computed tomography, or having high serum level of CA-125.

Method

After fulfilling the clinical data (including the age and menopausal status), all patient’s pelvises were examined by Prosound Alpha 7 ultrasound machine (Hitachi Aloka Medical America, Inc., Germany). We used transabdominal, transvaginal, or both approaches.

Gray-scale sonographic and Doppler data analysis

Each ovarian lesion was evaluated morphologically according to the following parameters: tumor volume more or less than $10 \text{ cm}^3$, solid component (not present, hyperechoic, non-hyperechoic), cystic component (not present, anechoic, echogenic), papillary
projection, septal thickness (not present, thin < 3 mm, thick ≥ 3 mm), and wall thickness (not identified, thin < 3 mm, thick ≥ 3 mm).

After morphological evaluation, color flow Doppler was activated. It was stated as having flow when the flow was central, and it was considered to have no flow when no signal could be detected or if the blood flow was peripheral. Once a central vessel was identified by the color Doppler US, the spectral Doppler parameters as resistive index (RI) and pulsatility index (PI) were automatically calculated. The lowest RI and PI were used for analysis, if there were more than one vessel within the lesion [9].

The following diagnostic algorithm was used:

Any mass has the following criteria: volume ≥ 10 cm³, non-hyperechoic solid component, papillary projection, septal thickness ≥ 3 mm, wall thickness ≥ 3 mm, mass with central blood flow and RI < 0.6, and PI < 1.6 were categorized as suspicious for malignancy [10].

The gold standard test for the benign lesions (as hemorrhagic cysts (Fig. 1)) was spontaneous resolution after 6–8 weeks of sonographic follow-up (n = 88). However, the gold standard test was a histopathological examination of all the malignant ovarian lesions (n = 53) and 15 benign ovarian lesions which have not typical signs of benignity. Tumors were classified according to the FIGO criteria [13] and staged according to WHO criteria [14].

Statistical analysis
Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in the form of mean ± SD or median (range), while nominal data were expressed in the form of frequency (percentage). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, positive likelihood ratio, and negative likelihood ratio for each sonographic and Doppler parameter were calculated using the ROC curve. Chi-square test was used to compare the nominal data of different groups in the study, while the student t test was used to compare the mean of different two groups and ANOVA tests for more than two groups. Multivariate regression analysis for predictor of ovarian malignancy was calculated; p value was significant if < 0.05.

Results
One hundred fifty six lesions were detected in the examined 116 women, and 103 (66%) lesions were benign and 53 (44%) lesions were malignant. Regarding the clinical data of the examined women, most of the malignant ovarian lesions were noted in older age than in benign lesions with < 0.001 p value and significant odds ratio = 1.45 (p = 0.04); also, the majority of the malignant ovarian lesions were in the postmenopausal women (n = 35, 66%), while most of the benign ovarian lesions were in the premenopausal women (n = 74, 71.8%) p < 0.001, but its odds ratio was insignificant (1.22, p = 0.4).

Fig. 2 A 55-year-old woman with GB adenocarcinoma on metastatic work up. a Transabdominal ultrasound shows non-hyperechoic soft tissue mass with cystic component within (white arrow). b Doppler ultrasound detects multiple central blood flow within the solid mass. c Spectral Doppler shows 0.3 RI and 0.5 PI. The histopathological examination after true-cut needle biopsy revealed metastatic adenocarcinoma.
Gray-scale US morphological feature analysis

All US features including tumor volume, tumor component, papillary projection, septal thickness, and wall thickness had a statistically significant difference between benign and malignant ovarian lesions; the $p$ value of each of them was < 0.001 except that of tumor volume was 0.02. Mean tumor volume was significantly larger in malignant ovarian lesions ($890.82 \pm 123.76$) in comparison to benign lesions ($798.32 \pm 187.69$) with insignificant odds ratio (0.56, $p = 0.06$). The majority of the malignant lesions had non-hyperechoic solid component (92.5%) (Fig. 2), and also it had the highest sensitivity, specificity, accuracy, PPV, NPV, and AUC in discrimination between benign and malignant ovarian lesions as demonstrated at Table 1 with 19.45 odds ratio ($p = 0.01$) in predicting ovarian cancer, while the majority of benign lesions had no solid component (92.2%). The presence of papillary projection was noted in 83% of the malignant lesions with 4.56 odds ratio ($p = 0.02$) (Fig. 3), in contrast to 6.8% in benign lesions. Thick septation was noted in 53.8% of the malignant lesions with 3.45 odds ratio ($p = 0.04$) (Fig. 4); however, the cases of benign lesions had no or thin septa (97%). The absence of wall definitions and thick wall was present in 81% of the malignant lesions.

Doppler parameter analysis

Color Doppler shows neovascularity in 88.7% of the malignant ovarian lesions; 73.6% of them show central blood flow, in contrast to only 1.9% central flow in benign lesions (Table 2). From the logistic regression test, the new vascularity with central flow is a predictor of ovarian cancer with 7.55 odds ratio ($p = 0.04$). From Table 3, we noted that the diagnostic performance of RI < 0.6 was higher than PI at < 1.6 cutoff point.

| Table 1 | Diagnostic performance of the gray-scale US features |
|---------|------------------------------------------------------|
| Indices | Non-hyperechoic solid component | Cystic component | Papillary projection | Septal thickness |
| Sensitivity | 92.5% | 55% | 83% | 36% |
| Specificity | 97% | 68% | 93.2% | 97% |
| Positive predictive value | 94% | 47% | 86% | 86.4% |
| Negative predictive value | 96% | 75% | 91.4% | 75% |
| Positive likelihood ratio | 32 | 2 | 12 | 12 |
| Negative likelihood ratio | 0.08 | 0.67 | 0.18 | 0.76 |
| Accuracy | 94.8% | 62% | 88.4% | 82% |
| Are under the curve | 0.94 | 0.61 | 0.88 | 0.66 |
| $p$ value | < 0.001 | 0.03 | < 0.001 | 0.04 |

$p$ value was significant if $< 0.05$

Discussion

US plays an important role in the identification and characterization of ovarian lesions. Thus, several studies have been conducted in the world to evaluate the role of
the gray-scale and Doppler US in the characterization of benign and malignant ovarian lesions [10, 11], but the results have been conflicting.

We found that the age was the most important clinical risk factor for ovarian cancer as we noted from the multivariate regression test with 1.45 odds ratio, and also the risk of ovarian cancer increases in postmenopausal women than in premenopausal women, as between the 53 malignant ovarian lesions, 35 patients (66%) were in the post menopause; however, 71.8% of the benign

Fig. 4 A 48-year-old woman with accidentally discovered right ovarian lesion on ultrasound. a Transabdominal ultrasound shows cystic lesion with multiple thick septa (white arrow); it measures 10 cm × 7 cm × 6 cm, b while spectral Doppler ultrasound detects blood flow within the central portion of the septa and shows 0.5 RI and 0.6 PI. The histopathological examination after laparoscopy revealed serous cystadenoma
ponents, papillary projection, thick internal septa ≥ volume > 890.82 ± 123.76, non-hyperechoic solid component that the malignant ovarian lesions show large tumor ovarian lesions. From these US features, we concluded significant difference between the benign and malignant ovarian lesions. From the logistic regression test, we concluded that the presence of central blood flow was a significant predictor of ovarian cancer with 7.55 odds ratio. These results were concordant with the results of the studies done by Brown et al. [15], Valentin et al. [16], and Herrmann et al. [17], which demonstrated that the non-hyperechoic solid component feature has long been recognized as strongly associated with malignancy in both gross pathologic and sonographic feature. Also, Khurana et al. [10] reported that the papillary projections was a predictor of malignancy.

Timmerman et al.’s [18] and Granberg et al.’s [19] results were agreed with our results in that the presence of thick septation was the significant predictor or risk factor for ovarian cancer as we reported in our study that its odds ratio was 3.45.

In our study, color Doppler allows mapping of the blood flow within the mass and shows neovascularity in 88.7% of malignant lesions and central blood flow in 73.6% of these lesions, but 98% of the benign ovarian lesions show peripheral or absent blood flow; these results correlated well with the study done by Khurana et al. [10] who reported that the detection of the blood flow has consistently related to the malignant ovarian lesions as 97.5% neovascularity could be seen in the malignant ovarian lesions. Also, our results agreed with the results of the study that was done by Barroilhet et al. [4] who demonstrated that the central blood flow concerning malignancy and the absence of blood flow or peripheral blood flow almost suggest the benignity and rolled out the malignancy as the central blood flow in their study was identified in 75.9% of the malignant ovarian lesions. From the logistic regression test, we concluded that the presence of central blood flow was a significant predictor of ovarian cancer with 7.55 odds ratio.

Spectral Doppler can measure the blood flow indices to determine the resistance within the vessels using the RI and PI. The values of RI and PI in our study were lower in malignant lesions (0.60 ± 0.18 and 1.6 ± 0.51, respectively) than in benign lesions (0.89 ± 0.17 and 2.54 ± 1.08, respectively). These results were in accordance with the data reported by Khurana et al. [10] in which the mean values of RI and PI for malignant lesions were less than for benign lesions. Despite the better diagnostic performance of the RI than PI in our study in discrimination between benign and malignant ovarian lesions, they observed only in 58.5% and 60.4% of malignant tumors, respectively. These results show low clinical values of the RI and PI as diagnostic tool used in differentiation between benign and malignant ovarian lesions. Ueland et al. [20] also concluded that the addition of Doppler US did not improve the diagnostic accuracy of ovarian lesions, and reported that the morphological features only are an accurate and inexpensive method used for

### Table 2 Doppler ultrasonographic findings of the ovarian lesions

|                      | Benign lesions (103) | Malignant lesions (53) | p value |
|----------------------|----------------------|------------------------|---------|
| Amount of flow       |                      |                        | < 0.001 |
| None                 | 67 (65%)             | 6 (11.3%)              |         |
| Scanty               | 36 (35%)             | 8 (15.1%)              |         |
| Moderate             | 0                    | 27 (50.9%)             |         |
| Abundant             | 0                    | 12 (22.6%)             |         |
| Location of the flow |                      |                        | < 0.001 |
| None                 | 67 (65%)             | 6 (11.3%)              |         |
| Peripheral           | 34 (34%)             | 8 (15.1%)              |         |
| Central              | 2 (1.9%)             | 39 (73.6%)             |         |
| Pulsatility index    | 2.54 ± 1.08          | 1.6 ± 0.51             | < 0.001 |
| Resistive index      | 0.89 ± 0.17          | 0.60 ± 0.18            | < 0.001 |

Data was expressed in the form of mean (SD), frequency (percentage). p value was significant if < 0.05.

lesions were in the premenopausal status. These results were concordant with the results of Khurana et al. [9] who reported that 68.6% of the benign lesions were in the premenopausal women.

All the gray-scale US features in our study show significant difference between the benign and malignant ovarian lesions. From these US features, we concluded that the malignant ovarian lesions show large tumor volume > 890.82 ± 123.76, non-hyperechoic solid components, papillary projection, thick internal septa ≥ 3 mm, and thick wall ≥ 3 mm. The presence of non-hyperechoic solid component followed by papillary projection shows the highest diagnostic performance of the ovarian lesion in comparison to the other US features with (92.5% vs 83%) sensitivity, (97% vs 93.2%) specificity, (94.8% vs 88.4%) accuracy, and (0.94 vs 0.88) AUC, respectively. Also, the non-hyperechoic solid component and papillary projection were the most consistent and significant predictors or risk factors for ovarian cancer with 19.45 and 4.56 odds ratio, respectively. These results were concordant with the result of the studies done by Brown et al. [15], Valentin et al. [16], and Herrmann et al. [17], which demonstrated that the non-hyperechoic solid component feature has long been recognized as strongly associated with malignancy in both gross pathologic and sonographic feature. Also, Khurana et al. [10] reported that the papillary projections was a predictor of malignancy.

### Table 3 Diagnostic performance of pulsatility and resistive indices

| Indices                  | Pulsatility index | Resistive index |
|--------------------------|-------------------|-----------------|
| Sensitivity              | 79%               | 79%             |
| Specificity              | 84%               | 95%             |
| Positive predictive value| 86%               | 95%             |
| Negative predictive value| 75%               | 78%             |
| Positive likelihood ratio| 5                 | 15              |
| Negative likelihood ratio| 0.25              | 0.22            |
| Are under the curve      | 0.89              | 0.92            |
| Accuracy                 | 81%               | 88%             |
| Cutoff point             | < 1.6             | < 0.60          |
| p value                  | < 0.001           | < 0.001         |

*p value was significant if < 0.05*
this purpose. From our logistic regression test, we reported that the RI and PI were insignificant predictors. From our results, we reported that the color Doppler flow imaging should be used to evaluate the presence and location of flow in ovarian lesions without a need for RI or PI, as they had no more value than color flow Doppler in addition to its non-feasibility and the time-consuming [21].

This study has several limitations; firstly, we did not evaluate the CA-125 as a predictor of ovarian malignancy. Secondly, this study was done in ovarian lesions only not in adnexal masses. Thirdly, relatively smaller sample size relative to the previous studies, not being a multicentric study.

Conclusions
As evident from the above discussion, the golden results of our study is picking up three gray-scale US features as the non-hyperechoic solid component, papillary projection, thick septa, and one Doppler feature which is the central blood flow and one clinical feature which is the old age ≥ 52 years as predictors or risk factors for ovarian cancer. This diagnostic approach we apply is simple, rapid, and recommend that initial evaluation of the patient age should be done thoroughly, as it is an art that cannot be replaced by sophisticated diagnostic gadget and also concluded that the use of the spectral Doppler parameter as RI and PI has no more value in prediction of ovarian cancer and this will save time and money. In the absence of the above features, the risk of malignancy is low, and conservative management with follow-up scans may be appropriate.

Abbreviations
US: Ultrasonography; RI: Resistive index; PI: Pulsatility index; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under receiver operating curve

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Authors’ contributions
Corresponding Author: LMRK: Dr. Larinia was responsible for the study design, analysis, and interpretation of the data, editing, drafting, and submission of the manuscript. Guarantor of integrity of the entire study. Co-Author: HHMD: She was responsible for data acquisition and statistical analysis. GSS: She was responsible for the study concept, final approval, and revision of the manuscript before its submission. AS: She was responsible for the data acquisition and analysis, examination, and referral of all the patients to the radiodiagnosis department. MAA: He was responsible for the quality control of data and the accuracy of the references. MTH: She was responsible for revision all the pathological specimen after surgery, and writing the pathological part of the manuscript. All authors have approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of the Faculty of Medicine at Assiut University in Egypt in February 28, 2017, and its number is 17100016. Written informed consent was obtained from all patients to participate in this study.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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