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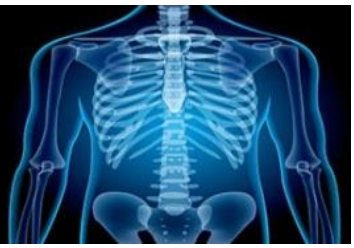

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Dr. George Lewiz Shenouda Ayad
Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo Governorate, Egypt

Dr. Saad Aly Abd Rabou
Professor, Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo Governorate, Egypt

Dr. Tarek Wahbi Hemeda
Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo Governorate, Egypt

Dr. Allam Elsayed Allam
Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo Governorate, Egypt

Corresponding Author:
Dr. Saad Aly Abd Rabou
Professor, Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo Governorate, Egypt

Role of dynamic contrast enhanced magnetic resonance imaging and diffusion weighted imaging in evaluation of ovarian tumors

Dr. George Lewiz Shenouda Ayad, Dr. Saad Aly Abd Rabou, Dr. Tarek Wahbi Hemeda and Dr. Allam Elsayed Allam

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Abstract
Background: Ovarian cancer has been a leading malignancy endangering women's health with high rate of worldwide prevalence. For the best possible outcome from treatment, the ovarian tumor must be accurately staged and characterized before surgery. To better characterize female pelvic masses, imaging techniques have developed significantly.
Objective: To assess the value of adding dynamic contrast enhanced (DCE) and diffusion weighted images (DWI) to the conventional magnetic resonance imaging (MRI) in the evaluation of ovarian cancer.
Patients and Methods: From January 2019 to March 2020, 50 patients with ovarian cancers participated in this prospective trial at Ain Shams university hospital.
Results: DWI MRI revealed diffusion restriction in 37 instances (78.7%) and facilitated diffusion in 10 cases (21.3%). the ADC value range (0.5 to 3.2) with a mean of 1.1 0.5. 16 instances (34%) out of the 47 cases displayed type 1 curves, 15 cases (31.9%) displayed type 2 curves, and 16 cases (34%) displayed type 3 curves. On histological diagnosis, type 1 curve cases all presented benign instances. There were statistically significant differences between the three diagnostic techniques and the pathological diagnosis. However, compared to conventional based diagnosis, diffusion-based diagnosis and perfusion-based diagnostic had greater AUC, sensitivity, specificity, and accuracy. Both perfusion- and diffusion-based diagnoses use the same values on the ROC curve.
Conclusion: The diagnostic accuracy of conventional MRI has significantly increased with the addition of DWI and DCE-MR sequences.

Keywords: Ovarian tumors, dynamic, radiodiagnosis

Introduction

Ovarian tumors are the fifth most common malignancy in women and the second most common gynecological tumor. They account for the fifth-highest percentage of mortality from cancer [1].

Whether an ovarian tumor is benign, borderline, or malignant, the treatment plan will vary. Consequently, preoperative characterization is important [2]. This is particularly important for young women who should be provided conservative surgery to protect their fertility [3].

Despite the algorithmic existence that consider clinical symptoms, CA125 (cancer antigen) serum determination and malignancy-related ultrasonographic indications [4], Preoperative characterization is still challenging, particularly for complicated lesions, and up to 25% of ovarian tumors are ultrasound-indeterminate and need further imaging [5].

MRI is a powerful tool for problem-solving and can provide information on surgical planning without exposing users to radiation. Malignant ovarian tumors are diagnosed with MRI, which can locate huge solid masses [6]. Previous research has shown that MRI technology can be used for preoperative diagnosis, accurately classifying ovarian tumors as benign or cancerous with a 91% accuracy rate [7, 8].

Dynamic contrast enhancement (DCE-MRI) offers superior functional imaging capabilities. It becomes a common diagnostic device for assessing the female pelvic [9]. The tumor vasculature inside a tumor microenvironment is also described using multiparametric estimations of permeability and perfusion. Malignant tumors have a larger circulatory system than benign tumors, thus they contrast more quickly and have stronger signals [10].

DWI is an MRI sequence that enhances peritoneal implant detection and delineation both during initial staging and follow-up. Additionally, it aids in distinguishing benign from malignant lesions and enhances the contrast among lesions and surrounding tissues. Moreover, DWI offers quantitative data on tissue cellularity that can be used to distinguish between living tumors and changes brought on by treatment [10, 11].

Cancers have displayed decreased ADC (Apparent Diffusion Coefficient) values when DWI is applied in gynecologic applications. ADC levels rise in carcinomas that react to radiation therapy, making it a useful biomarker for treatment response and for assessing recurrence and multi-focal tumors [10].

This study aim is to evaluate the benefit of combining DCE MRI and DWI MRI with the conventional MRI in the ovarian cancers evaluation.

Patients and methods

This prospective study was conducted at Ain Shams University Hospitals in Egypt from January 2019 to March 2020 on 50 patients with ovarian cancers. All participants in this study were given their signed consent after our institution's ethical committee gave its approval.

In the current study, patients with complicated ovarian related lesions, cystic lesions with solid vegetations, thick septa, or components of soft tissue, solid ovarian lesions, two adnexal lesions either suspicious or solid lesions were all considered. While we rolled out patients with 1) uncomplicated cystic ovarian lesions or 2) just fatty ovarian lesions. Individuals with impaired renal function, general MRI contraindications such as the presence of pacemakers or mechanical clips, or patients with claustrophobia were also excluded from the study.

Every patient has through a thorough history taking process, pelvic ultrasonography (trans-abdominal and/or trans-vaginal), MRI evaluation, and histopathological evaluation.

MRI protocol

The use of a 1.5 Tesla MR scanner was used for MR imaging (Ingenia, Philips Healthcare, Netherlands). All patients underwent a pelvic phased array coil scan while they were lying flat. Three common MRI sequences, axial, sagittal, and coronal T2WIs, were run on the female pelvis. Before administering the contrast agent, DWI was captured in the axial plane using a single shot echo-planar imaging sequence with the following parameters: b values (0, 800, 1000), TR/TE (2871/78), Slice thickness (5 mm), Gap (1.5 mm), FOV (RL 375 mm, AP 312 mm, FH 161 mm), and reconstruction matrix (124x105). High resolution isotropic volumetric examination was used for MR perfusion (THRIVE). Most frequently, an axial plane was selected, and the procedure was carried out on the appropriate plane that showed both the lesion and the myometrium on the same image.

Gadolinium chelate (Dimeglumine gadopentate, Magnevist; Germany) was administered at a dose of 0.2 ml per kilogramme of body weight using a power injector (Medrad, spectris solaris R) at a rate of 2 ml/sec. Next, 20 milliliters of normal saline were injected into the tubing to flush it. Images were captured one after the other every 14 seconds for a total of 420 seconds, start 14 seconds (first phase) before the bolus injection. 40 consecutive slices of 2 mm thickness were collected.

Interpretation of images

The captured images were transformed to (Philips 881030 Intelli-Space IX/LX Workstation).

a. Conventional sequences analysis

The lesion morphological characteristics, such as its laterality, related size, and complexity, were assessed using standard MRI sequences.

b. Analysis of DWI

Qualitative analysis

While most malignant masses have high intensity of signal on DWI and low signal in the related ADC maps, the majority of benign masses have low intensity of signal on DWI and high signal in the associated ADC maps (facilitated diffusion) (limited diffusion).

Quantitative analysis

The ROI was manually selected on the solid and cystic parts of the tumors after the ADC map was created, and the workstation then automatically computed the ROI to get the ADC calculated values.

c. Dynamic contrast enhancement (DCE) analysis

On the DCE MR sequence, two areas of interest were set on the exterior myometrium and the ovarian mass's solid tissue that showed the greatest contrast. Using a colored workstation-generated map with the highest level of improvement, the most enhanced solid part was identified. The classification of the solid tissue augmentation was categorized using a previously defined time-signal intensity curve:

1. A type 1 curve was defined as a steady rise in the intensity of the solid tissue signal without a distinctly marked shoulder.
2. A type 2 curve was known as an early, modest rise in the signal strength of solid tissue in comparison to the myometrium, succeeded by a plateau.
3. A type 3 curve was characterized by an early elevation in the solid tissue related signal intensity that was steeper than the myometrium's.

From quantitative data, maximum of all relative enhancements (MRE), Maximum enhancement (SImax), wash in rate (WIR) and wash out rate (WOR) were analyzed.

Statistical analysis: The SPSS software for Windows v. 20 was used to conduct statistical analysis (SPSS Inc., Chicago, IL). The statistical reporting of data used the terms range, mean, standard deviation, frequencies (number of occurrences), and percentage when applicable. To compare numerical quantitative data, Kruskal Wallis and Mann Whitney tests were used. Comparing qualitative data was done using the Fisher exact test. The effectiveness of the investigated diagnostic test in predicting malignancy was described using sensitivity, specificity, overall accuracy, negative and positive predictive values. A probability value ($p=0.05$) was evaluated for significance using statistics. The ROC curve was used to determine the cutoff values for the semiquantitative parameters.

Results

The study involved 50 female patients in total. On

histological examination, three of them were discovered to have non-ovarian malignancies; two had tubo-ovarian abscesses, and one had a cyst accompanied with hemorrhagic infarction. Those three cases were left out of the study to avoid bias. The data documented from 47 cases was analyzed. Their median age was 39.9 15.9 years, with a range of 12 to 70. Thirty patients (63.82%) were pre-menopausal, compared to 17 patients (36.17%) who were post-menopausal. Pelvic pain was the primary presenting symptom in 30 instances (63.8%). The histopathological diagnosis of the lesions is shown in Table 1.

Conventional MRI analysis

The average size of the ovarian tumors according to conventional MRI was 10.62 6.3 cm. Out of the 47 instances, 4 cases (or 8.5%) only revealed bilateral disease, whereas the remaining 43 cases (or 91.5%) revealed unilateral pathology. The pathological tumor types (benign, malignant, and borderline) did not differ statistically significantly in terms of size, bilaterality of the lesion, or ancillary abnormalities on conventional MRI.

Diffusion weight images MRI analysis

DWI MRI revealed diffusion restriction in 37 instances (78.7%) and facilitated diffusion in 10 cases (21.3%). the ADC value range (0.5 to 3.2) with a mean of 1.1 0.5. Regarding diffusion limitation and ADC value, there was a difference that was statistically highly significant among the pathogenic forms of tumors (p 0.001 for both).

The ROC curve involved area under the curve (AUC) is used to predict malignancy based on DWI was higher for the ADC value than for diffusion restriction (Table 2). The accuracy of predicting malignancy based on the ADC value and diffusion restriction is 90.7% and 81.4%, respectively. Less than 1x10-3 mm2/sec is the ADC cutoff value below which malignancy is anticipated.

Dynamic contrast enhanced MRI analysis

From the 47 cases, type 1 curves were present in 16 (34%) cases, type 2 curves in 15 (31.9%) cases, and type 3 curves in 16 (34%) cases. On histological diagnosis, type 1 curve cases all presented benign instances. The pathogenic types of the tumors and the curve type differed statistically significantly. Curve types 2 and 3 accurately predict the chance of malignancy with 95.35% accuracies, 88.89% sensitivity, and 92.6% specificity. For curves 2 or 3, the negative predictive value is 100%. (Table 3).

Regarding MRE%, there was a difference of no statistical significance found among the pathological diagnoses. While the pathological diagnosis of SI max, WIR, and WOR showed statistically significant differences. To assess the AUC for each distinct perfusion parameter, a ROC curve was built. When employing WOR, SI max, and then WIR, the least overlap and greatest AUC were seen. This offers the most accurate enhancing information for identifying benign from borderline/cancerous tumors. 100% sensitivity, specificity, NPV, PPV, and accuracy were generated by using the WOR>6 cutoff value. (Table 3).

Table 1: Histopathological diagnosis of the lesions

Type	Benign (n= 18)	Borderline (n= 4)	Malignant (n= 25)	Total
Epithelial tumors	*Serous tumors: 3 cases (6.3%). *Mucinous tumors: 3 cases (6.3%)	*Serous tumors: 3 cases (6.3%). *Mucinous tumors: 1 case (2.1%)	*Serous tumors: 6 cases (12.7%). *Mucinous tumors: 3 cases (6.3%). *Brenner's tumor: 2 cases (4.2%). *Clear cell carcinoma: 1 case (2.1%). *Undifferentiated carcinoma: 1 case (2.1%). *Endometroid carcinoma: 1 case (2.1%).	24 cases (51.1%)
Sex cord stromal tumors	*Fibrothecoma/ fibroma: 4 cases (8.5%). *Benign sclerosing tumor of the ovary: 1 case (2.1%).		*Granulosa cell tumor: 3 cases (6.3%).	8 cases (17%)
Germ cell tumors	*Mature cystic teratoma: 4 cases (8.5%). *Struma ovarii: 3 cases (6.3%).		*Immature teratoma: 4 cases (8.5%) *Dysgerminoma: 4 cases (8.5%).	15 cases (31.9%)

Table 2: ROC curve analysis for prediction of malignancy according to diffusion restriction and ADC value (reference test is the pathological diagnosis; Reference groups is benign).

	Diffusion restriction	ADC value
Optimal cutoff point	Restricted	≤ 1
AUC (Area Under Curve)	0.778	0.969
95% CI (Confidence Interval)	0.625-0.890	0.865-0.998
P value	<0.001*	<0.001*
Sensitivity	100	100
Specificity	55.56	77.78
PPV (Positive Predictive Value)	75.8	88.9
NPV (Negative Predicative Value)	100	93.7
Accuracy	81.4	90.7

*: Significant level at *p*-value < 0.05

Table 3: ROC curve analysis for prediction of malignancy according to curve type and semi-quantitative assessment of perfusion (reference test is the pathological diagnosis; Reference groups is benign)

	Curve type		SI max	WIR	WOR
Optimal cutoff point	2 or 3	3	>1285	>17.9	>6
AUC (Area Under Curve)	0.948		0.978	0.936	1
95% CI (Confidence Interval)	0.834-0.992		0.879-1	0.817-0.988	0.918-1
P value	<0.001*		<0.001*	<0.001*	<0.001*

Sensitivity	100	56	100	92	100
Specificity	88.89	94.44	94.44	94.44	100
PPV (Positive Predictive Value)	92.6	93.3	96.2	95.8	100
NPV (Negative Predicative Value)	100	60.7	100	89.5	100
Accuracy	95.35	72.1	97.67	93.02	100

*: Significant level at *P* value < 0.05

Relation of conventional, diffusion, perfusion and combined diagnosis with pathological results

In ROC curve analysis, malignancy was predicted based on conventionally based diagnosis. (Figure 1), diffusion-based diagnosis (Figure 2) and perfusion-based diagnosis (Figure 3). Between the three diagnostic techniques and the pathological diagnosis, there were statistically significant differences. However, compared to conventional based diagnosis, diffusion and perfusion-based diagnostic had greater AUC, sensitivity, specificity, and accuracy. Both perfusion- and diffusion-based diagnoses use the same values on the ROC curve.

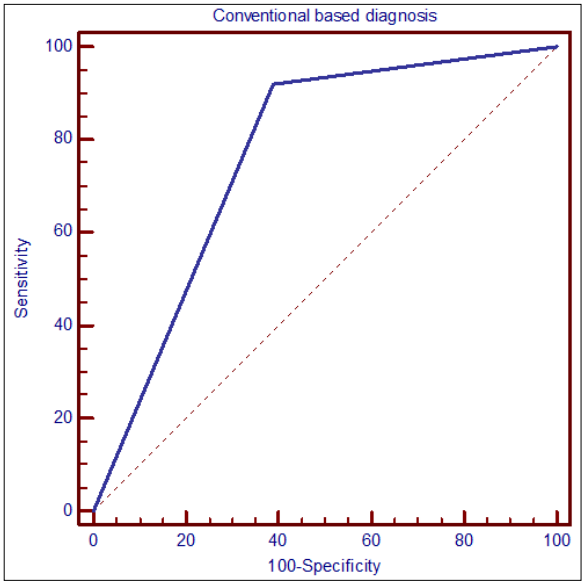

Fig 1: ROC curve analysis for conventional MRI in predicting malignancy (reference test is the pathological diagnosis; Reference groups is benign).

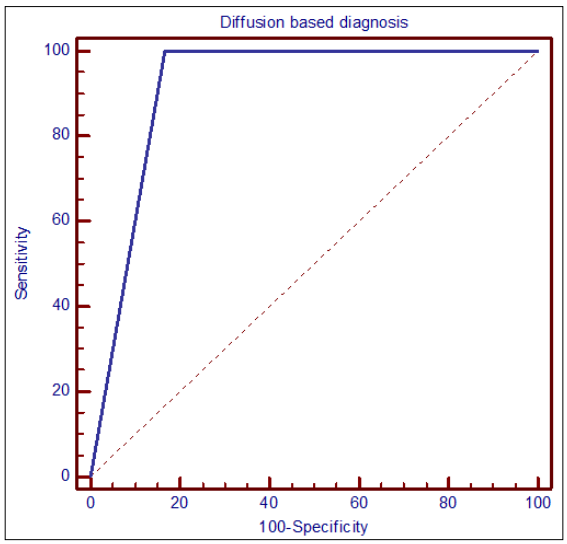

Fig 2: ROC curve analysis for DWI-MRI in predicting malignancy (reference test is the pathological diagnosis; Reference groups is benign).

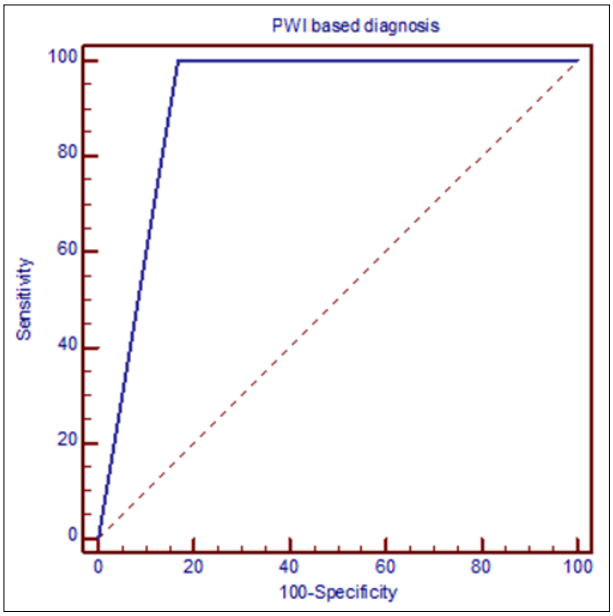

Fig 3: ROC curve analysis for PWI-MRI in predicting malignancy (reference test is the pathological diagnosis; Reference groups is benign).

Discussion

Recently, functional techniques like MR dynamic contrast-enhanced imaging and MR diffusion have been put to the test to boost MRI's sensitivity, specificity, and accuracy in order to increase diagnostic confidence [12]. This study's objective is to assess the additional value of DCE-based perfusion and DWI MRI over traditional MRI imaging for characterizing ovarian cancers.

As conventional MRI using axial T1 and T1 fat suppression, axial, sagittal and coronal T2 s in malignant epithelial ovarian tumors ($0.841 \pm 0.209 \times 10^{-3}$ mm^2/s) [13]. In this study, there was a difference of no statistical significance among borderline epithelial ovarian tumors and malignant tumors of epithelial ovarian regarding their appearance on DWI as well as the mean ADC values. This can be explained by the small number of borderline epithelial ovarian tumors within the sample (4 cases only) in comparison with the MEOTs (14 cases).

In a different study by Zhao *et al.* 2018 [14], The effectiveness of the ADC value in separating benign from malignant sex cord stromal ovarian tumors was examined in 85 individuals with ovarian tumors. They presume that the benign ovarian tumors had an ADC mean value of about 1.28 0.23 10-3 mm2/s while the malignant ovarian tumors had an ADC mean value of about 0.86 0.17 10-3 mm2/s. Compared to our study, the measurements for malignant lesions were very close to our measurements while the measurements for benign lesions were lower than our measurements. This can be explained by the difference in sample size [14].

Perfusion MR based on DCE is used for characterization of ovarian tumors. DCE-MRI has been added to the ESUR recommendations for imaging adnexal lesions because it

provides a more accurate qualitative assessment of enhancement than standard CE sequences [15].

It was previously common practise in several clinical settings to analyse the TIC type, notably when determining the difference between malignant and benign tumours in breast and prostate cancer [16]. Despite this, ovarian cancers were rarely diagnosed with TIC [17].

During our analysis, curve type I was discovered to be 100% specific for benign ovarian type of cancer (all cases displaying type I curve were benign). The type II and type III curves favored borderline/malignant tumors more. There was only one benign case of curve type III, and it was an ovarian benign sclerosing tumor, according to pathology. This result is due to the fact that sclerosing stromal tumors are much more vascular and show ecstatic blood vessels under microscopy than myometrium with a distinct shoulder, which causes a rapid increase in signal intensity.

It has to be noted that curve type III was also present in the two eliminated instances with tubo-ovarian abscess. The same explanation for the related hyperemia and vascular congestion in the area also applies to this situation.

Our findings are comparable to those of Hai-Ming Li *et al*. [18] who found that the TIC type was effective at differentiating between malignant and benign ovarian tumors, nonetheless, there was a substantial overlap among the borderline and malignant tumors [18].

According to the proposed pathophysiology of tumor growth idea, tumors must stimulate angiogenesis in order to proliferate. The vessels are highly permeable to a variety of macromolecules due to the wide gaps among the endothelial cells, the endothelium, and also the basement membranes, as well as among the basement membranes and the angiogenetic arteries involved pericytes produced by tumors. DCE-MRI can use these characteristics to its advantage. Differential enhancement is created when MR contrast chemicals, which leak slowly through healthy blood arteries, flow through tumor vessels more quickly. The tumor microcirculation can be functionally examined because of how quickly the contrast is washed in and out [19].

In our investigation, among the perfusion parameters, WOR, WIR, and SImax showed the biggest differences among benign and malignant lesions (p values 0.001). WOR (100%), SImax (97%) and WIR (93%) were the three metrics' highest accuracy levels.

In our investigation, a value of >6 was the cutoff for WOR (WOR greater than 6 indicates the likelihood of malignant lesions). NPV and PPV were both 100%. It is crucial to note that the count of eliminated cases with tubo-ovarian abscesses who also had WOR was greater than six can also be accounted for by the presence of concomitant hyperemia.

According to a theory, washout rate merely reflects the capillary wall's permeability property and has no bearing on the density of the small blood vessels. The most widely recognised theory behind WOR's highest diagnostic precision is this one [19].

In 2003, Sohaib *et al*. [20] investigated the percentage rise in the intensity of the signals of the solid parts of adnexal masses at 60 sec (early) and 120 sec (late) of enhancement. They discovered that, when compared to benign lesions, malignant lesions exhibit higher enhancement during the early enhancement phase than the late enhancement phase [20]. This illustrates how crucial SImax is for distinguishing between benign and malignant tumors when it is shown in the early dynamic phases.

Our investigation's threshold value for SI max was >1285. (Malignant tumors are those whose SI max is greater than that value.). 100% sensitivity and 94% specificity were measured. Although those measurements conflict with those results, Dilks *et al*. suggested a threshold value of >250 for malignancy prediction with a 100% sensitivity and specificity [21]. Given that the cases in our analysis were distributed unequally, this disparity can be explained. We had 18/47 benign cases and from the 18 benign cases there are 8 cases with high SImax raising the cut off value in our study (4 cases fibroma/fibrothecoma, 2 cases benign sclerosing tumor and 3 cases mucinous cystadenoma). In this context, It's crucial to note that the SImax values for the two tubo-ovarian abscess cases that were omitted were high.

In our investigation, As assessed by sensitivity, specificity, NPV, PPV, and accuracy (92%, 94%, 89.5%, 95.8%, and 93%, respectively), WIR underperformed WOR and SImax.

WIR was cut off at >9.5 by Bernardin *et al*. (Malignant lesions are those that have a WIR of 9.5 or higher) [3]. The cut off value of ourstudy (>17.9) was greater than that value, which is also comprehensible given the study's unequal distribution of cases and larger-than-average proportion of individuals with hyper vascular characteristics.

There are several limitations to our study. the study's inclusion of pathologies with an uneven distribution. Ovarian metastasis was one reasonably prevalent pathogenic entity that was left out of the investigation. The study also involves a small case number having epithelial borderline ovarian tumors. Young patients of reproductive age make up the bulk of epithelial borderline tumor cases; therefore, to preserve fertility, a cautious surgical approach rather than a radical one may be indicated. Additional research including more samples and better pathological distribution is advised.

We should mention that our study excluded other non-ovarian adnexal lesions as tubo-ovarian abscess which is not rare in clinical practice. Addition of those cases to the study will be valuable.

Moreover, literature showed that DCE has a very important role in differentiating ovarian fibromas from subserous leiomyomas and this entity was not included in the study.

Other aspect of limitation was technical aspect including that the myometrium should be included at the same image with the ovarian mass which is not always possible. In this situation, oblique views may be used.

Additionally, the approach of ROI drawing may be susceptible to human error, which could have an impact on performance. Complex masses with varying tissue compositions were present in some of our patients, which may have affected the ROI placement choice and readings.

Conclusion

In conclusion, the diagnostic accuracy of conventional MRI has significantly increased with the addition of DWI and DCE MR sequences. DCE MRI offers extra details on tumour vascularity.

Conflict of Interest

Not available

Financial Support

Not available

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